FORMULATION AND EVALUATION OF" EMTRICITABINE AND TENOFOVIR-DISOPROXIL FUMARATE" IMMEDIATE RELEASE FILM COATING TABLETS

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Submitted by

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DECLARATION

The thesis entitled **"FORMULATION AND EVALUATION OF EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE IMMEDIATE RELEASE FILM COATED TABLETS"** was carriedout by the author in Department of Pharmaceutics, C.L.Baid Metha Collegeof Pharmacy, Chennai – 96 during the academic year 2011-2012. The work embodiedin this thesis is original, and is not submitted in part or full for any other degree of thisor any other University.

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ABBREVATIONS

S.NO	ABBREVATIONS	EXPANSION
1	API	Active pharmaceutical ingredient
2	GIT	Gastro intestinal track
3	PEG	Poly ethylene glycol
4	HAART	Highly active antiretroviral therapy
5	DDS	Drug Delivery system
6	IR	Immediate Release
7	CR	Controlled Release
8	PVP	Polyvinylpyrrolidone
9	SLS	Sodium Lauryl Sulphate
10	NARTIs	Nucleoside analogue reverse transcriptase inhibitor
11	HIV	Human immune virus
12	AIDS	Acquired immuno deficiency syndrome
13	NNRTI	Non-nucleoside reverse transcriptase inhibitor
14	DNA	Deoxyribonucleic Acid
15	EC_{50}	Effective Concentration
16	CCR_5	Human Chemokinage Receptor
17	CD_4	Cluster Of Differentiation 4
18	ICH	International Conference on Harmonization
19	AST	Aspartate Amino Transferase
20	ALT	Alanine Transaminase
21	GT	Glutamyl Tran peptidase
22	HBV	Hepatitis B virus

23	ECB	Emtricitabine
24	USP	United States Pharmacopoeia
25	ND	Not Detected
26	BP	British Pharmacopoeia
27	PDR	Pysician Desk Reference
28	RS	Related substances
29	A	Appearance
30	#	Mesh No
31	%	Percentage
32	^{0}C	Degree centigrade
33	HDPE	High density poly ethylene
34	TDF	Tenofovir Disoproxil Fumarate
35	MCC	Micro Crystalline Cellulose
36	SSF	Sodium Steryl Fumarate
37	HPC	Hydroxy Propyl Cellulose
38	DCP	Di Calcium Phosphate
39	^{0}F	Degree Fahrenheit
40	IP	Indian pharmacopoeia
41	Ml	Milliliter
42	Mg	Milligram
43	µl	Micro liter

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1. INTRODUCTION

1.1TABLETS [1,2]

Definition: Tablets are tamperproof solid unit dosage forms containing medicament or mixture of medicaments and excipients compressed or molded into solid cylindrical shape having either flat or convex surfaces.

1.2Properties of tablets

The attributes of an acceptable tablet are as follows:

- The tablet must be sufficiently strong and resistant to shock, abrasion, should withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
- Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.
- The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels in the blood after its administration.
- Tablets must be elegant in appearance, characteristic shape, color and other markings necessary to identify the product.
- Tablets must retain all these functional attributes which include drug stability and efficacy.

1.3 ADVANTAGES AND DISADVANTAGES

Advantages

- Offers greatest capability of all oral dosage forms for the greatest dosage precision &Good content uniformity.
- High patient compliance.
- Their cost is lowest of all dosage forms
- One of the major advantages of tablet over capsules is that the tablet is essentially "tamperproof dosage form".
- Easiest and cheapest to packaging and shipment

- They are having best combined properties of chemical, mechanical and microbiological properties
- Accuracy of dose is maintained since tablet is a solid unit dosage forms
- Longer expiry period and minimum microbial spillage owing to lower moisture content
- Large scale manufacturing is feasible in comparison to other dosage forms. Therefore, economy can be achieved.
- Organoleptic properties (taste, appearance, and odor) are improved by coating of the tablets. Product identification is easy and marketing done with the help of grooved punches and printing with edible ink.
- As a tablet is not a sterile dosage form, stringent environmental conditions are not required in the tablet department.

Disadvantages

- Some drugs resist compression owing to their amorphous nature & low density character.
- Drugs with poor wetting, slow dissolution property, large dosages or any combination of these features may be difficult or impossible to formulate & manufacture as a tablet.
- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Slow onset of action as compared to parenterals, liquid orals and capsules.
- The amount of liquid drug (e.g., vitamin E, Simethicone) that can be trapped into a tablet is very less.
- Difficult to swallow for kids, terminally ill and geriatric patients.
- Patients undergoing radiotherapy cannot swallow tablet.

1.4 TYPES AND CLASSES OF TABLETS[(2)]

Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, by their form and method of manufacture.

1.4.1 TABLETS INGESTED ORALLY

(a) Compressed tablets

These tablets are uncoated and made by compression of granules. These tablets are usually intended to provide rapid disintegration and drug release. These tablets contain water-soluble drugs, which after swallowing get disintegrated in the stomach, and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body.

(b) Multiple compressed tablets

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeat action prolonged action products. To avoid incompatibility, the ingredients of the formulation except the incompatible materials are compressed into a tablet then incompatible substances along with necessary excipients are compressed tablet.

(c)Multilayered tablets

These tablets consist of two or more layer of materials compressed successively in the same tablets. The color of each layer may be the same or different. The tablets having layers of different colours are known as "multicoloured tablets".

(d) Sustained action tablets

These tablets are used to get a sustained action of medicament. These tablets when taken orally release the medicament in a sufficient quantity as and when required maintaining the maximum effective concentration of the drug in the blood throughout the period of treatment

(e) Enteric-coated tablets

These are compressed tablets meant for administration by swallowing and are designed to bypass the stomach and get disintegrated in the intestine only. These tablets are made to release the drug undiluted and in the highest concentration possible within the intestine. Eg: tablets containing anthelmentics, and amoebic id

(f) Sugar coated tablets

The compressed tablets having a sugar coating are called " sugar coated tablets".

(g) Film coated tablets

Application of thin polymer based coatings to tablet/granules by a spray atomization technique. Thickness of such coating is usually between 20-100µm .

(h) Chewable tablets

These tablets are chewed in the mouth and broken into small pieces. In this way, the disintegration time is reduced and the rate of absorption of the medicament is increased. e.g.: aluminium hydroxide tablets, and phenolphthalein tablets.

1.4.2 TABLETS USED IN ORAL CAVITY

(a) Buccal tablets

These tablets are to be placed in the buccal pouch or between the gums and lips or cheek where they dissolve or disintegrate slowly and are absorbed directly without passing into the alimentary canal. Eg: tablets of ethisterone

(b) Sublingual tablets

These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT.
Eg: tablets of glyceryl trinities.

(c) Lozenge and torches

These tablets are designed to external local effect in the mouth or throat. These tablets are commonly used to treat sore throat or to control coughing in common cold. They may contain local anaesthetics antiseptic, antibacterial agents, astringent and antitussives.

1.4.3 TABLETS USED TO PREPARE SOLUTION[2]

(a) Effervescent tablets

In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric acid or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as disintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble. Tablet triturates usually are made from moist material, using a triturate mild that gives them the shape of cut sections of cylinder. Such tablets must be completely and rapidly soluble, The problem arising from the compression of these tablets is the failure to find a lubricant that is completely water-soluble.

(b) Dispensing tablets

These tablets provide a convenient quality of potent drug that can be incorporated readily in to powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are, supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

(c) Hypodermic tablets

Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most new drug substances, there is no justification for the hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia

1.4.4 INSERTED TABLETS[2]

(a) Dental cones

These are relatively minor compressed tablets meant for placing them in the empty socket-after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow releasing antibacterial compounds or to

reduce bleeding by containing the astringent. These cones generally get dissolved in 20 to 40 min time.

(b) Implantation tablets

These tablets are placed under the skin or inserted subcutaneous by means of minor surgical operation and are slowly absorbed. These implants must be sterile and should be packed individually in sterile condition. Implants are mainly used for administration of hormones such as testosterone, and deoxycorticosterone etc.

(c) Vaginal tablets

These tablets are meant to dissolve slowly in the vaginal cavity. These tablets are typically ovoid or pear shaped to facilitate retention in the vagina. This tablet form is used to release steroids, antibacterial agents, antiseptics or astringents to treat vaginal infections.

The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration that is, the drug delivery system should delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment.

1.5 ORAL DRUG DELIVERY[3]

This is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process.

For many drug substances conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with an acceptable level of safety to the patient.

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery

and development of new drug entities, pharmaceutical formulations, mainly because of patient compliance and convenience in administration.

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms is the difficulty to swallow.

Oral dosage form is the most popular route for drug therapy. Over 80% of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost.

1.5.1 Current technologies in oral drug delivery[3]

Over the last 3 decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced DDS are manufactured or fabricated in traditional pharmaceutical formulations, such as Tablets, Capsules, Sachets, Suspensions, Emulsions, and Solutions, they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities.

Based on the desired therapeutic objectives, oral DDS may be assorted into three categories:

- **Immediate-release preparations,**
- **Controlled-release preparations and**
- **Targeted- release preparations.**

Immediate-Release Preparations[4]

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastricabsorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden.

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, crosscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or Shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying.

Controlled-Release Preparations (CR)

The currently employed CR technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

Targeted-Release Preparations

Site-specific oral drug delivery requires spatial placement of a drug delivery device at a desired site within theGgastro Intestinal (GI) tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and the small and large intestines. The latter requires consideration of both longitudinal and transverse aspects of GI constraints.

1.6 MANUFACTURING METHODS[2,5]

There are four general methods of tablet preparation.

- Direct compression
- Wet granulation method
- Dry granulation method
- Fluidized bed granulation

In the tablet-pressing process, it is important that all ingredients be dry, powdered, and of uniform grain size as much as possible. The main guideline in manufacture is to ensure that the appropriate amount of active ingredient is equal in each tablet so ingredients should be well-mixed. Compressed tablets are exerted to great pressure in order to compact the material. If a sufficiently homogenous mix of the components cannot be obtained with simple mixing, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to prepare powders for granulation into a tablet: wet granulation and dry granulation.Powders that can be mixed well do not require granulation and can be compressed into tablets through Direct Compression.

Direct Compression

This method is used when a group of ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. This is not very common because many tablets have active pharmaceutical ingredients which will not allow for direct compression due to their concentration or the excipients used in formulation are not conducive to direct compression.

Granulation is the process of collecting particles together by creating bonds between them. There are several different methods of granulation. The most popular, which is used by over 70% of formulation in tablet manufacture is wet granulation. Dry granulation is another method used to form granules.

Wet granulation

Wet granulation is a process of using a liquid binder or adhesive to the powder mixture. The amount of liquid can be properly managed, and over wetting will cause the granules to be too hard and under wetting will cause them to be too soft and

friable. Aqueous solutions have the advantage of being safer to deal with than solvents.

- Procedure of Wet Granulation
- Step 1: Weighing and Blending - the active ingredient, filler, disintegration agents, are weighed and mixed.
- Step 2: The wet granulate is prepared by adding the liquid binder/adhesive. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia and cellulose derivatives such as methyl cellulose, CMC, gelatin, and povidone. Ingredients are placed within a granulator which helps ensure correct density of the composition.
- Step 3: Screening the damp mass into pellets or granules
- Step 4: Drying the granulation
- Step 5: Dry screening: After the granules are dried, pass through a screen of smaller size than the one used for the wet mass to select granules of uniform size to allow even fill in the die cavity
- Step 6: Lubrication- A dry lubricant, antiadherent and glidant are added to the granules either by dusting over the spread-out granules or by blending with the granules. Its reduces friction between the tablet and the walls of the die cavity. Antiadherent reduces sticking of the tablet to the die and punch.
- Step7: liquid binder, but sometimes many actives are not compatible with water. Water mixed into the powder can form bonds between powder particles that are strong enough to lock them in together. However, once the water dries, the powders may fall apart and therefore might not be strong enough to create and hold a bond.

Dry granulation

This process is used when the product needed to be granulated may be sensitive to moisture and heat. Dry granulation can be conducted on a press using slugging tooling or on a roller compactor commonly referred to as a chilsonator. Dry granulation equipment offers a wide range of pressure and roll types to attain proper densification.

However, the process may require repeated compaction steps to attain the proper granule end point. It requires drugs or excipients with cohesive properties.

- Some granular chemicals are suitable for direct compression (free flowing) e.g. potassium chloride.
- Tableting excipients with good flow characteristics and compressibility allow for direct compression of a variety of drugs.

Fluidized bed granulation

It is a multiple step process performed in the same vessel to pre-heat, granulate and dry the powders. It is today a commonly used method in pharmaceuticals because it allows the individual company to more fully controls the powder preparation process. It requires only one piece of machinery that mixes all the powders and granules on a bed of air.

1.7 EXCIPIENTS USED IN TABLETS[6]

Excipients are inert substances used as diluents or vehicles for a drug. In the pharmaceutical industry it is a catch all terms which includes various sub- groups. Comprising diluents or fillers, binders or adhesives, disintegrants, lubricants, glidants or flavours, fragrances and sweeteners. All of these must meet certain criteria as follows:-

- They must be physiological inert.
- They must be acceptable to regulatory agencies
- They must be physiologically and chemically stable.
- They must be free of any bacteria considered to be pathogenic or otherwise objectionable.
- They must be not interfere with the bioavailability of the drug.
- They must be commercially available in the form and purity commensurate to pharmaceutical standards.
- Cost must be relatively inexpensive.

To assure that no excipient interferences with the utilization of the drug, the formulator must carefully and critically evaluate combinations of the drug

with each of the contemplated excipients and must ascertain compliance of each ingredient with existing standards and regulations.

The screening of drug-excipients and excipient-excipient interactions should be carried out routinely in preformulations studies.

Fillers (Diluents)

Tablet fillers of comprise a heterogeneous group of substances. Since they often comprise the bulk of the tablet, selection of a candidate from this group as a carrier for a drug is of prime importance.

Binders

Binders are the glue that holds powders together to form granules. They are the adhesives that are added to tablet formulations to provide the cohesiveness required for that bonding together of the granules under compaction to form a tablet. The quantity used and the method of application must be carefully regulated, since the tablet must remain intact when swallowed and then release its medicament.

Lubricants

Lubricants are used in tablet formulation to ease the ejection of the tablet from the die, to prevent sticking of tablets to the punches, and to prevent excessive wear on punches and dies. They function by interposing a film of low shear strength at the interface between the tablet and the die wall and the punch face.

In selecting a lubricant, the following should be considered:

- Lubricants markedly reduce the bonding properties of many excipients.
- Over blending is one of the main causes of lubrication problems. Lubricants should be added last to the granulation and tumble-blended for not more than 10 min.
- Lubricant efficiency is a function of particle size; therefore, the finest grade available should be used and screened through a 100-300 mesh screen before use.
- Examples of lubricants commonly used are magnesium stearali acid, talc, starch.

Disintegrants

Disintegrants are used in tablet preparation to break the tablet faster. But some of the disintegrants are also having property of enhancing solubility of insoluble drug.

Examples

- Crospovidone: Crospovidone is disintegrant, crospovidone also enhances solubility.
- Sodium starch glycollate: sodium starch glycollate is widely used in oral pharmaceuticals and as a disintegrant in capsule.

Glidants

Glidants are materials that improve the flow characteristics of granules by reducing the inter particulate friction. In proper amounts they also serve to assure smooth and uniform flow at all times.

Many of the excipients commonly used in tablet formulations are especially applicable for use in chewable tablets due to their ability to provide the necessary properties of sweetness and chewabilty. In general; these fall into the sugar category, although a combination of excipients with artificial sweeteners may provide a satisfactory alternative.

MISCELLANEOUS

Wetting Agents

Wetting Agents in tablet formulation aid water uptake and thereby enhancing disintegration and assisting in drug dissolution. Incorporation of anionic surfactant like Sodium Lauryl Sulphate (SLS) is known to enchance the dissolution. It has been established that SLS improves permeation of drug biological membrane since it destroys the path through which drug has to pass and thus minimizing the path length for the drug to travel. Wetting agents are mainly added when hydrophobic drug is to be formulated into tablet. SLS, Sodium disobutylsulfosuccinate are used as wetting agent in tablet formulation.

Dissolution Retardants

Dissolution Retardants are incorporated into tablet formulation only when controlled release of drug is required. Waxy materials like stearic acid and their esters can be used as dissolution retardants.

Dissolution Enhancers

They are the agents that alter the molecular forces between ingredients to enchance the dissolution of solute in the solvent. Fructose, Povidone, Surfactants are used as dissolution enhancer.

Adsorbents

Adsorbents are the agents that can retain large quantities of liquids. Therefore liquids like Vitamin E can be incorporated into tablets by addition of adsorbents. Most commonly used adsorbents in pharmaceuticals are anhydrous calicium phosphate, starch, magnesium carbonate, bentonite, kaoline, magnesium oxide. Generally the liquid to be adsorbed is first mixed with the adsorbent prior to incorporation into the formulation.

Buffers

Buffers are added to maintain a required pH since a change in pH may cause significant alteration in stability. Most commonly used buffering agent in tablet formulation includes sodium bicarbonate, calcium carbonate, and sodium citrate.

Antioxidants

Antioxidants are added in tablet formulation to protect drug from undergoing oxidation. Antioxidants undergo oxidation in place of drug or they block the oxidation reaction or they act as synergisys to other antioxidants.

Chelating Agents

Chelating agents tend to form complexes with trace amount of heavy metals ions inactivating their catalytic activity in the oxidation of medicaments.

Ethlenediaminetetracetic acid and its salts, Dihydroxy Ethyl Glycerin, Citric Acid and Tartaric Acid are most commonly used chelators

Flavors

Flavours are added to tablet formulation in order to make them enough in case of chewable tablet by improving the taste. Flavours are commonly used to improve the taste of chewable tablets as well as mouth dissolved tablets. Flavours are incorporated either as solids (spray dried flavours) or oils or aqueous (water soluble) flavors.

Sweeteners

Sweeteners are added to tablet formulation to improve the taste of chewable tablets. Sweeteners used in tablet formulation- Mannitol, Lactose, Sucrose, Dextrose, Saccharin, Cyclamate, Aspartame etc.

1.8 TABLET COATING[7,8]

Coated tablets are defined as the covered with one/more layers of mixtures of various substances such as natural waxes authorized colouring materials. coating may also contain active ingredient. Substances used for coating are usually applied as solution/suspension under condition where vehicle evaporates.

Why Tablet Coating is required?

A number of reasons can be suggested:

- The core contains a material which has a bitter taste in the mouth or has an unpleasant odour.
- Coating will protect the drug from the surroundings with a view to improve its stability.
- Coating will increase the ease by which a tablet can be ingested by the patient.
- Coating will develop the mechanical integrity; means coated products are more
  resistant to mishandling (abrasion, attrition etc.)

- The core contains a substance which is incompatible in the presence of light and
  subject to atmospheric oxidation, i.e. a coating is added to improve stability.
- The core alone is inelegant.
- The active substance is coloured and migrates easily to stain hands and clothes.
- The coated tablets are packed on high-speed packaging machine. Coating reduces
  friction and increases packaging rate.
- Coating can modify the drug release profile, e.g., enteric coating, osmotic pump,
  pulsatile delivery.

1.8.1 Types of coating[7,8]

- Sugar coating
- Film coating
- Enteric coating
- Controlled release coating
- Specialized coating
- Compressed coating
- Electrostatic coating
- Dip coating
- Vacuum film coating

1.8.2 FILM COATING[7,8]

Film coating is the process whereby a tablet, capsule, or pellet is surrounded by a thin layer of polymeric material.Film coated tablets are compressed tablets with a thin layer of suitable polymer capable of forming a skin like film over the tablet. The polymeric substance most commonly used are hydroxyl propyl methyl cellulose, hydroxyl methyl cellulose, The film is usually colored and has the advantage over sugar coating in that it is more durable, less bulky, and less time consuming to apply.

The film coating protects the medicament from the atmospheric effects. By its composition the coating is designed to rupture & expose the core tablet at the desired location with in GIT.

Table-1Reasons for Filmcoating

Reasons for film coating include	
Appearance	To change the color, for branding purposes or other aesthetic reasons
Stability	To protect the active ingredient from moisture, light, and/or the acidic environment of the stomach
Taste/odor Masking	To provide an easy to swallow tablet without the bitter taste of many actives
Release characteristics	Many film coating materials have functional properties which enable the delayed (enteric) release of dosage forms

Process Description

Film coating is a deposition of a thin layer of polymer surrounding the tablet core .Conventional pan equipments may be used but now a days more sophisticated equipments are employed to have high degree of automation of coating time. The polymer is solubilized into solvent, other additives like plasticizer &pigments are added. Resulting solution is sprayed on to a rotated tablet bed. The drying conditions cause removal of the solvent, giving thin deposition material around each tablet core.

Process Details

Usually spray process is employed in preparation of film coated tablet. Accelacota is the type of prototype of perforated cylindrical drum providing drying air capacity. Fluidized bed equipment has made considerable impact where tablets are moving in a stream of air passing through the perforated bottom of a cylindrical column with a smaller cylindrical insert the stream of cores is rising in the centre of device together with spray mist applied in the middle of the bottom. For fluidized coating very hard tablet hardness above 20 N have to be used.

Materials used in film coating

- Opaquent extenders
- Miscellaneous coating solution components

Examples of film formers

Hydroxyl propyl methyl cellulose (HPMC),Methyl hydroxyl ethyl cellulose (MHEC),Ethyl cellulose (EC),Hydroxyl propyl cellulose (HPC), sodium carboxyl methyl cellulose (CMC), Acrylate polymers, Povidone**.**

Advantages

- It is less time consuming technology.
- Not much labour is required.
- No adverse effect on Disintegration time of tablet.
- Production cost is low because material used for coating is cheap.
- Protects drug from atmospheric changes such as light, air, moist.

1.8.3 Immediate Release Film Coating Systems for Tablets[9,10,11]

Colorcon, the innovator and industry standard for complete film coating systems, offers a range of custom pigmented and non-pigmented film coatings for immediate release solid dose applications. film coating formulas produce attractive, elegant coatings on even the most challenging tablet surfaces and can be used in both aqueous and organic coating procedures.

An extensive selection of polymer blend formulations provides the user with the ability to impart

many beneficial features to a solid oral dosage formulation. Benefits include:

• Reduced coating process time

• Superior adhesion on difficult to coat cores

• Less stressful processing conditions for heat sensitive, friable or high drug contentcores

• Sharper logo definition, even at higher weight gains

• Better gloss and smoothness compared to conventional film coatings

• Improvedcolor stability

Aqueous film coating is the quickest and least expensive method for enhancing your tablet appearance and, unlike other methods, will not affect dissolution or disintegration profiles. dry-blend systems consist of polymers, plasticizers and pigments, combined in one, easy-to-use, dry powder system which is rehydrated quickly and simply with water. Colorcon also offers customized colour selection and colour matching of our immediate release tablet film coating products.

Celeron's ongoing research of film coating polymers has produced many enhanced polymer combinations resulting in new tablet coating options for our customers. Our newly developed, dry coating technology provides benefits such as improved adhesion, reduced processing times, and application of the tablet coating at wider process parameters. Advances in our immediate release tablet film coating technology not only give a more elegant appearance to your solid oral dosage form, but provide unique.

Figure-1 Film coating Tablets

1.8.4 Film Coatings for Every Application[9,10]

Colorcon offers a wide range of film coating products, many of which can be formulated specifically for your application and regulatory requirements. Whether the desired function for your tablet or particulate is immediate release, delayed (enteric) release and/or extended (controlled) release, the tablet film coating technology needed to enhance, protect, and modify the functionality of product.

Immediate Release

A distinctive product appearance offers many benefits to the producers and marketers of pharmaceutical tablets and nutritional supplements. Film coating is the most economical method of enhancing your product – improving visual appearance, as well as easing swallow ability, and enhancing the taste and masking objectionable odors. Colorcon film coatings can impart mechanical integrity, color, gloss, pearlescence or moisture protection to create an immediate release tablet that is both memorable and effective.

Extended Release

The extensively used polymer for extended release coating was Ethyl cellulose.

Application of an ethyl cellulose film from aqueous dispersion or organic solution provides the formulator the means to control the release of drug from a tablet or multiparticulatevia diffusion of the drug through the ethyl cellulose film. Novel means of controlled release can also be achieved using a combination of Colorcon's modified release coating systems.

Delayed Release

The enteric/delayed release products can help the deliver of final product that saves you development, scale-up and production time while assuring the integrity of the coating for the safety and efficacy of your finished dosage form. Various systems are available based on a variety of delayed release polymers for aqueous or organic processing to provide targeted release at various pH conditions.

For the solid dosage manufacturer, tablet film coating technology conveys many benefits including improved packaging efficiency, prevention of cross contamination and reduced tablet breakage and chipping. A large variety of pigmented and non-pigmented tablet film coating systems available. Which is cost Effective, protect from light moisture and environmental gases.

1.9 IMMEDIATE RELEASE DRUG DELIVERY SYSTEM[9,10,11]

Immediate release drug delivery system is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features.

These are the dosage forms in which ≥ 85% of labelled amount dissolves with in 30 min. However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release the active drug which then become available in whole or in part, for absorption from gastrointestinal tract.

1.9.1 Mechanism of drug release[10,11]

On exposure to aqueous fluids, hydrophilic matrices take up water and the polymer starts hydrating to form a gel layer. Drug release is controlled by diffusion barriers/ by surface erosions. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer comes in to contact with an aqueous medium, there is an abrupt change from a glassy to rubbery state associate with swelling process with time, water infiltration deep in to a case increasing the thickness by the gel layer. The outer layer becomes fully hydrated and starts dissolving or eroding. When water reaches the center of the system and the concentration of drug falls below the solubility value, the release rate of the drug begins to reduce. At the same time an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

1.9.2 Advantages of immediate release drug delivery system

- Release the drug immediately.
- More flexibility in adjusting the dose.
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem
- Immediate release drug delivery systems can be used in both
  initial stage and final stage of disease.

1.9.3 Super disintegrants in immediate release

These are especially important for an immediate release product where rapid release of dug substance is required. A disintegrant can be added to powder blend for direct compression.

Table-2 Super Disintegrants

Super disintegrants	Example	Mechanism of action	Special comment
Crosscarmellose	Crosslinked Cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.	-Swells in two dimensions. -Direct compression or granulation
Crosspovidone	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Pre Gelatinized Starch	Starch 1500	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix

1.9.4 MECHANISM OF TABLET DISINTEGRATION[12]

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of disintegration of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The tablet breaks to primary particles by one or more of the mechanisms:

- capillary action (Wicking)
- swelling
- Due to deformation
- Due to release of gases

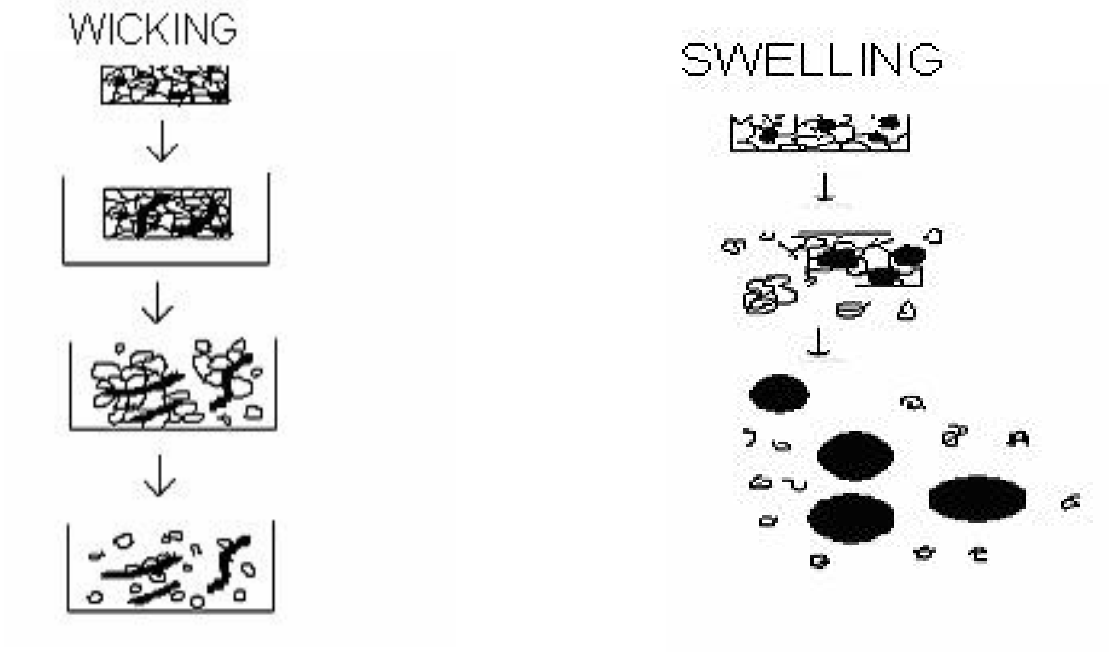
Capillary action (Wicking)

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides way for the penetration of fluid into tablets. The disintegrant particles (with cohesiveness and compressibility) themselves act to enhance porosity and provide these capillaries into the tablet. Liquid is drawn up or leak into these ways by capillary action and rupture the inter-particulate bonds causing the tablet to break into small particles

Swelling

Not all disintegrants swell in contact with water swelling is believed to be a mechanism in which; certain disintegrating agents (like starch) impart their disintegrating effect. By swelling on contact with water the adhesiveness of other ingredients in a tablet is overcome causing the tablet to disintegrate.

Figure-2 Mechanism Of Disintegration By Wiciking and Swelling



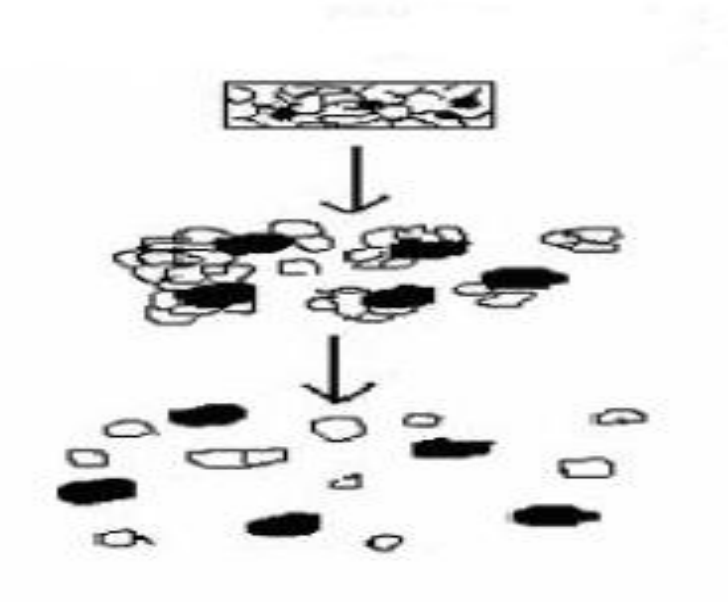
Water is pulled into pores by disintegrants and reduces the physical bonding between particles.

Particles swell and break up the matrix from within; swelling sets up; localized stress spreads throughout the matrix.

Deformation.

Starch grains are generally thought to be “elastic” in nature that is the grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression force involved in tabletting, these grains are permanently deformed and are said to be “Energy Rich” with these energy being released upon exposure to water, i.e. the ability for starch to swell is higher in “Energy Rich starch” grains than in starch grains that have not been deformed under pressure. It is believed that no single mechanism is responsible for the action ofmost disintegrants. But rather, it is more likely the result of inter-relationships between these major mechanisms

Figure-3 Mechanism of tablet disintegration by deformation



Particles swell to precompression size and break up the matrix

Release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when we needs to formulate very rapidly dissolving tablets or fast disintegrating tablet.

1.10 INTRODUCTION TO AIDS/HIV[13,14,15,16,17]

The virus infects the lymphocytes, the brain cells and macrophages. The illness is due to a single defect, viz destruction of the helper T lymphocytes (CD4) by the replicating virus particles, and impairment offunctioning of the surviving CD4 cells.
The patient therefore suffers from a specific defect in the cellular arm of the immune system. Cardiovascular and kidney has been reported.
The incubation period is estimated to be 1 to 7 years (means 4.5 years) Antibodies to HIV develop in 2-8 weeks after infection.

1.10.1Treatment

Current treatment for HIV infection of highly active antiretroviral therapy, or HAART. This has been highly beneficial to many HIV-infected individuals since its introduction in 1996, when the protease inhibitor-based HAART initially became available. Typically, these classes are two nucleoside analogue reverse transcriptase inhibitors (NARTIs or NNRTI).

1.10.2Classification of Drugs[14,17,18,19]

Drugs used against the retrovirus in AIDS

1. Nucleoside and Nucleotide reverse transcriptase inhibitors(NRTI)
2. Non- Nucleoside reverse transcriptase inhibitors(NNRTI)
3. Protease inhibitors
4. Integrase inhibitors
5. Viral entry inhibitors
6. Viral assembly inhibitors

1) Nucleoside and Nucleotide reverse transcriptase inhibitors(NRTI)

Their intended therapeutic action is to prevent the formation of HIV DNA by inhibiting HIV reverse transcriptase. Ex: Zidovudine, Stavudine, Didanosine, Zalcitabine, Abacavir, Emtricitabine and Azidothymidine (nucleosides) and Tenofovir (nucleotide).

2) Non- Nucleoside reverse transcriptase inhibitors (NNRTI)

Unlike the nucleoside analogs, the NNRTIs interfere with HIV-1 reverse transcriptase by noncompetitively binding directly to the enzyme downstream from the active catalytic site. Ex: Nevirapine, Efavirenz and Delaviridine.

3) Protease inhibitors

This protease cleaves multidomain viral proteins into their active forms; blocking this process completely would prevent the virus from being infectious. Ex: saquinavir, Ritonavir, Indinavir, Nefinavir and Lopinavir.

4)Integrase inhibitors

Multiple steps in the integration process are catalyzed by HIV-1 integrase. The integration of HIV-1 DNA into the host chromosome is achieved by the integrase performing a series of cutting and joining reactions. Integrase inhibitors seek to block the integrase enzyme from allowing this integration process from happening. Ex: Raltegravir

5) Viral entry inhibitors

An infectious HIV-1 virion consists of a nucleoprotein core surrounded by a lipid bilayer membrane derived from the cell that produced the virion. The virus membrane and plasma membrane of the host cell represent physical barriers between the core and its destination. To breach these barriers, enveloped viruses have evolved genes encoding proteins that catalyze the fusion of viral and cellular membranes and thereby place the core in the host cell cytoplasm. Ex: Enfuvirtide.

6) Viral assembly inhibitors

Assembly and release of HIV-1 are governed by the viral gag and vpu proteins. Following its synthesis in the cytosol, gag is rapidly and specifically transported to the site of virus assembly. The goal of these inhibitors is to block assembly or release by binding to one of these components.

2. AIM AND OBJECTIVE

AIM

- The aim of present work is to formulate film coated tablets of Emtricitabine combination with Tenofovir disoproxil fumaratetablets comparable to the marketed product.

OBJECTIVE

- To develop a pharmaceutically stable, cost effective and quality improved formulation of Emtricitabine combination with Tenofovir disoproxil fumarat**e** tablets.
- To study the release profile of the dosage form and to compare their drug-release profiles with the innovator.
- To determine the best fit dissolution profile for dosage form.
- To study the stability of dosage form and compare with the specification .
- The physical parameters evaluation, in-vitrodrug release studies and stability studies are conducted to justify the formulation efficacy.

3. LITERATURE SURVEY

1.**Takuma Shirasaka.,*et al*.,(**2011) studied the the incidence of FTC-associated SP in Japanese patients was 3.9%, and was comparable to the previously reported incidence in Asian patients (4%). FTC-associated SP was not associated with any clinically significant symptoms and has little clinical significance. [20]

2.DanielDrogan.,*et al*.,(2010)Studied the suppression of drug-sensitive viruses is significantly enhanced by FTC compared to 3TC. Mathematical modeling of the distinct rates of suppression of drug-sensitive viruses revealed an approximately 3-fold higher antiretroviral potency for FTC compared to 3TC. [21]

3. Alessandro Soria.,*et al*.,(2010) Studied that Once-weekly emtricitabine led to a higher viral rebound than once-daily monotherapy, but similar immunological changes, thus suggesting a role of M184V in slowing the decrease in CD4% in treatment failing subjects. [22]

4.**Abhay Gupta.,*et al*.,(**2009) the correlation between disintegration and dissolution for immediate release tablets containing a high solubility drug and to identify formulations where disintegration test, instead of the dissolution test, may be used as the acceptance criteria based on International Conference on Harmonization guidelines. [9]

5. **Julia Krause.,*et.al*.,(**2009) Studied The preparation ofimmediate release pellets with solid lipid binders through a solvent-free cold extrusion/spheronisation process was investigated in this study pellets showed favourable properties like spherical shape, narrow size distribution, a high drug load of 80% sodium benzoate and a drugrelease of more than 90% within 40 min.. [23]

6.LaurenceBousquet.,*et al*.,(2008) studied Emtricitabine has both inhibitor and substrate characteristics with MRP1 in PBMCs in vitro, and does not interact with PI accumulation. [24]

7.Chee-Kin Hui.,*et al*.,(2008)Combination ADV plus FTC resulted in more potent suppression of HBV DNA over 96 weeks of therapy. [25]

8.**Jessica Tan.,*et al*.,(**2008) Discussed thatTDF monotherapy is effective for patients with virologic breakthrough or suboptimal response to ADV, but combination therapy with a nucleoside analogue should be considered in patients with ADV-resistance. [26]

9.**Giordano Madeddu,,*et al*.,(**2008) studied Both prevalence and incidence of nephrotoxicity were low in patients receivingtenofovir in a non-selected clinical setting. Renal injury in patients receivingtenofovir seems associated with the presence of co-morbidities and with advanced HIV infection [27]

10.**Giuseppe Gumina**., ***et al*.,(**2007) told thatCurrently, two L-nucleosides, lamivudine and emtricitabine, are available for the treatment of human immunodeficiency virus and hepatitis B virus infections, and several other analogs, such as clevudine and troxacitabine, are in advanced clinical trial development stages. [28]

11. **Sabah Souliman.,*et al*.,(**2006) Investigated to USP II method, the novel in vitro model demonstrated a high level of efficacy in mimicking the behaviour of acetaminophen IR tablets in vivo in fasted and fed states. [10]

12. **Gail Skowronet.,*et al*.,**(2006)demonstrate the Short-term monotherapy studies have demonstrated that emtricitabine 200 mg QD reduces HIV RNA levels by 1.7 to 1.92 $\log_{10}$ copies/mL. Current US DHHS and IAS-USA guidelines support emtricitabine as a recommended component of an initial antiretroviral regimen [18]

13. **Robert G. Gish.,*et al*.,(**2005) discussed that Emtricitabine was well tolerated and demonstrated a potent antiviral response for up to 2 years in patients with chronic hepatitis B infection. Based on these data, 200 mg emtricitabine once daily was chosen as the optimal dose for future hepatitis B studies. [11]

14. **Tomas Cihlar.,*et al*.,(**2005) studied tenofovir exhibited weak cytotoxic effects in all cell types tested with less in vitro cytotoxicity than the majority of NRTIs currently used for the treatment of HIV disease. [29]

15. **George M. Szczech.,*et al*.,(**2003)Reproductive and developmental toxicology studies were conducted with emtricitabine, a nucleoside analog in development for treatment of human immunodeficiency virus (HIV) (Phase III) and hepatitisB(HBV) (Phase III) infections. The development and fertility of F1 progeny were unaffected by emtricitabine in a mouse pre- and post-natal study. These data demonstrate a favorable pre-clinicalreproductive safety profile for emtricitabine. [30]

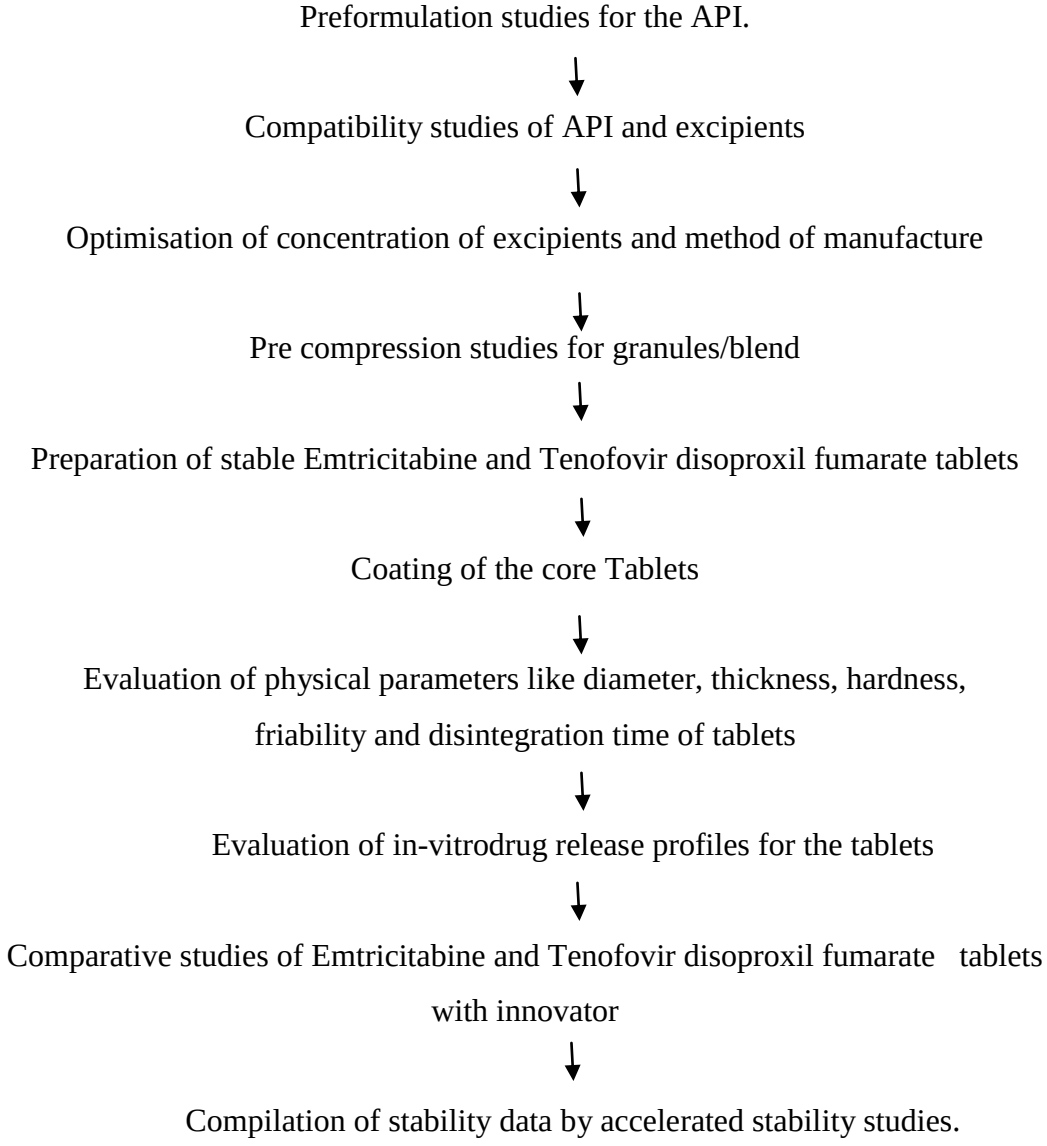
16. **Horatio B. Fung.,*et al*.,(**2002) studied tenofovir DF has exhibited anti-HIV activity invarious HIV-infected cell lines and has produced a synergistic or additive effect against HIV when combined with other antiretroviral agents, tenofovir DF appears to be a promising agent for the treatment of HIV infection. [19]

17. **Montaner**.**J.S.G.,*et al*.,(**1999) Currently available antiretrovirals require combination therapy with at least three agents to achieve the goal of suppressing viral replication to as low as possible. [16]

18.Komal F. Chopra.,*et al*.,(1997) investigated that Early initiation of treatment with multidrug therapy in all individuals infected with HIV is recommended by most experts with the common goal of reducing, viral load to a nondetectable level. Numerous studies have shown the increased efficacy of multidrug therapy over monotherapy.[17]

4. PLAN OF WORK

Process Flow Chart



5. DRUG PROFILE

5.1 Emtricitabine[11,31,32,33]

Chemical Name [IUPAC Name]

The chemical name is 4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one

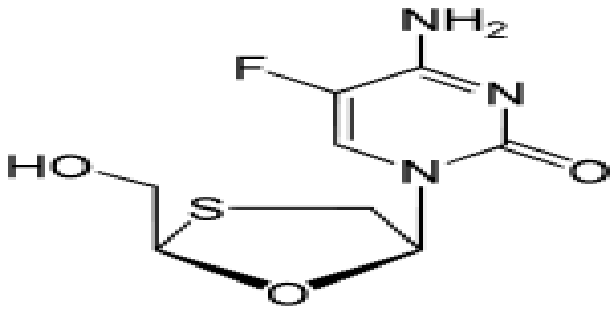
Molecular Formula

The empirical formula of Emtricitabine is $C_8 H_{10} F N_3 O_3 S$

Molecular Weight

The molecular weight is 247.248

Structural Formula



PHYSICOCHEMICAL PROPERTIES

Colour **:**It isawhite to off-white powder.

Solubility **:**Emtricitabine has is a solubility of approximately 112 mg/mL in water 25 ° C.

Classification Code **:** Anti-Infective Agents; Antiretroviral ; Antiviral Agents ; Antiviral[treatment of HIV-1 and hepatitis B infections]

pKa **:**2.65

Meltingpoint **:**136-140°C

PolarSurfaceArea **:**79.67 $Å^2$

IndexofRefraction **:**1.731

MolarRefractivity	**:**54.01cm^3
MolarVolume	**:**135.1cm^3
SurfaceTension	**:**72.8yne/cm
Density	**:**1.82g/cm^3
FlashPoint	**:**221.9°C
EnthalpyofVaporization	**:**80.89kJ/mol
BoilingPoint	**:**443.3°Cat760mmHg
Vapour Pressure	**:** 1.01E-09 mmHg at 25°C

DOSAGE AND ADMINISTRATION

Recommended Dose

Emtricitabine may be taken without regard to food.

Adult Patients (18 years of age and older)

- Emtricitabine capsules: one 200 mg capsule administered once daily orally.
- Emtricitabine oral solution: 240 mg (24 mL) administered once daily orally.

INTERACTIONS

Emtricitabine is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Additional important information regarding the use of Emtricitabine for the treatment of HIV-1 Infection:

Dosage Forms And Strengths

- Emtricitabine is available as capsules and oral solution.
- Emtricitabine capsules, containing 200 mg of emtricitabine.
- Emtricitabine oral solution is a clear, orange to dark orange liquid containing 10 mg of emtricitabine per mL.

MICROBIOLOGY

Mechanism of Action

Emtricitabine, a synthetic nucleoside analog of cytidine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viralDNA which results in chain termination..

Antiviral Activity

The antiviral activity in cell culture of emtricitabine against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% effective concentration (EC_{50}) value for emtricitabine was in the range of 0.0013-0.64 µM (0.0003-0.158 µg/mL).

Resistance

Emtricitabine-resistant isolates of HIV-1 have been selected in cell culture and *in vivo*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a substitution in the HIV-1 reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).

CLINICAL PHARMACOLOGY

Mechanism of Action

Emtricitabine is an antiviral drug.

Pharmacokinetics

Absorption

Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1-2 hours post-dose. The mean steady state plasma trough concentration at 24 hours post-dose was 0.09 µg/mL.

Distribution

In vitro binding of emtricitabine to human plasma proteins was < 4% and independent of concentration over the range of 0.02-200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

Metabolism

In vitro studies indicate that emtricitabine is not an inhibitor of human CYP450 enzymes. Following administration of ^{14}C-emtricitabine, complete recovery of the dose was achieved in urine (~86%) and feces (~14%). Thirteen percent (13%) of the dose was recovered in urine as three putative metabolites. The biotransformation of emtricitabine includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable.

Elimination

The plasma half-life of emtricitabine is approximately 10 hours. The renal clearance of emtricitabine is greater than the estimated creatinine clearance, suggesting elimination by both glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

DRUGINTERACTIONS

The potential for drug interactions with EMTRIVA has been studied in combination with zidovudine, indinavir, stavudine, famciclovir, and tenofovir disoproxil fumarate. There were no clinically significant drug interactions for any of these drugs.

The following are adverse reactions:

- Lactic acidosis/severe hepatomegaly with steatosis
- Severe acute exacerbations of Hepatitis B
- Immune reconstitution syndrome.

5.2TENOFOVIR DISOPROXIL FUMARATE[(31,33,34,35)]

Chemical Name [IUPAC Name]

The chemical name is ({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]oxy} methyl) phos phonic acid.

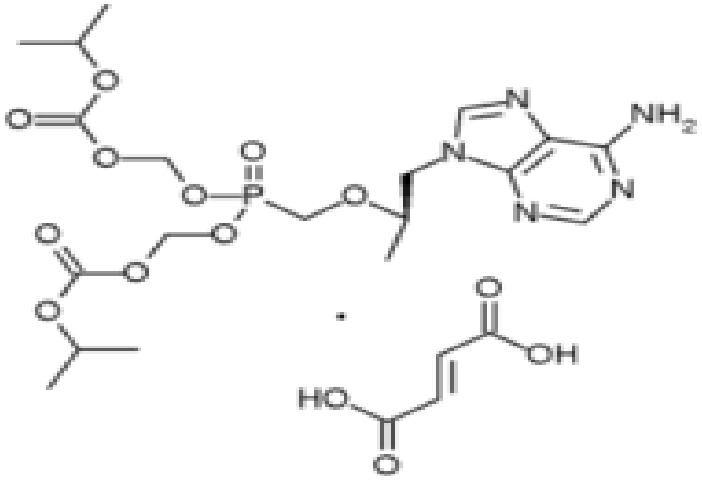
Molecular Formula

The empirical formula of Tenofovir disoproxil fumarate is $C_{19}H_{30}N_5O_{10}P \bullet C_4H_4O_4$

Molecular Weight

The molecular weight is 635.52

Structural Formula



Physicochemical properties: It isawhite to off-white crystalline powder.

Solubility	**:** Tenofovir disoproxil fumarate e has is a solubility of approximately 13.4 mg/mL in distilled water at 25°C.
pKa	**:**2.65
Polar Surface Area	**:**172.47 ?2
Flash Point	**:** 342.5 °C ;
Enthalpy of Vaporization	**:** 94.85 kJ/mol ;
Boiling Point	**:** 642.7 °C at 760 mmHg ;
Vapour Pressure	**:** 2.06E-16 mmHg at 25°C

The Tenofovir disoproxil fumarate has a brand name VIREAD. It is obtained from a fumaric acid salt of bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Tenofovir disoproxil fumarate is converted to tenofovir, which is an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5'-monophosphate. Tenofovir exhibits activity against HIV-1 reverse transcriptase. Tenofovir disoproxil fumarate is taken orally .

INTERACTIONS

Tenofovir disoproxil fumarate is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

DOSAGE AND ADMINISTRATION

Recommended Dose

For the treatment of HIV-1 or chronic hepatitis B.The dose of Tenofovir disoproxil fumarate is 300 mg once daily taken orally, without regard to food.

SIDE EFFECTS

The following adverse reactions are discussed in other sections of the labeling:

- Lactic Acidosis/Severe Hepatomegaly with Steatosis
- Severe Acute Exacerbation of Hepatitis New Onset or Worsening Renal Impairment Decreases in Bone Mineral Density
- Immune Reconstitution Syndrome

ADVERSE REACTIONS

Immune System Disorders

allergic reaction, including angioedema

Metabolism and Nutrition Disorders

lactic acidosis, hypokalemia, hypophosphatemia

Respiratory, Thoracic, and Mediastinal Disorders

dyspnea

Gastrointestinal Disorders

pancreatitis, increased amylase, abdominal pain

Hepatobiliary Disorders

hepaticsteatosis, hepatitis, increased liver enzymes (most commonly AST, ALT gamma GT)

Skin and Subcutaneous Tissue Disorders

rash

Musculoskeletal and Connective Tissue Disorders

rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

Renal and Urinary Disorders

acute renal failure, renal failure, acute tubular necrosis, Fanconi syndrome, proximal renal tubulopathy, interstitial nephritis (including acute cases), nephrogenicdiabetes insipidus, renal insufficiency, increased creatinine, proteinuria, polyuria

The following adverse reactions, listed under the body system headings above, may occur as a consequence of proximal renal tubulopathy: rhabdomyolysis, osteomalacia, hypokalemia, muscular weakness, myopathy, hypophosphatemia.

DRUG INTERACTIONS

This section describes clinically relevant drug interactions with VIREAD. Drug interactions studies are described elsewhere in the labeling

Didanosine

Coadministration of Tenofovir disoproxil fumarate and didanosine should be undertaken with caution and patients receiving this combination should be monitored closely for didanosine-associated adverse reactions. Didanosine should be discontinued in patients who develop didanosine-associated adverse reactions

Atazanavir

Atazanavir has been shown to increase tenofovir concentrations The mechanism of this interaction is unknown.

Lopinavir/Ritonavir

Lopinavir/ritonavir has been shown to increase tenofovir concentrations The mechanism of this interaction is unknown.

CLINICAL PHARMACOLOGY

Mechanism of Action

Tenofovir disoproxil fumarate is an antiviral drug.

Pharmacokinetics

The pharmacokinetics of tenofovir disoproxil fumarate have been evaluated in healthy volunteers and HIV-1 infected individuals. Tenofovir pharmacokinetics are similar between these populations.

Absorption

Tenofovir disoproxil fumarate is a water soluble diesterprodrug of the active ingredient tenofovir. The oral bioavailability of tenofovir from Tenofovir disoproxil fumarate in fasted subjects is approximately 25%.

The pharmacokinetics of tenofovir are dose proportional over a Tenofovir disoproxil fumarate dose range of 75 to 600 mg and are not affected by repeated dosing.

Distribution

In vitro binding of tenofovir to human plasma or serum proteins is less than 0.7 and 7.2%, respectively, over the tenofovir concentration range 0.01 to 25 μg/mL.

Metabolism and Elimination

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. There may be competition for elimination with other compounds that are also renally eliminated.

MICROBIOLOGY

Mechanism of Action

Tenofovir disoproxil fumarate is an acyclic nucleoside phosphonatediesteranalog of adenosine monophosphate. Tenofovir disoproxil fumarate requires initial diester hydrolysis for conversion to tenofovir and subsequent phosphorylations by cellular enzymes to form tenofovirdiphosphate, an obligate chain terminator. Tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α, β, and mitochondrial DNA polymerase γ.

Activity against HIV

Antiviral Activity

The antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes.

Resistance:HIV-1 isolates with reduced susceptibility to tenofovir have been selected in cell culture. These viruses expressed a K65R substitution in reverse transcriptase and showed a 2–4 fold reduction in susceptibility to tenofovir.

6.EXCIPIENT PROFILE

6.1 STARCH 1500[36]

Nonproprietary Names

BP: Pregelatinised Starch PhEur: Starch, Pregelatinised USP-NF: Pregelatinized Starch

Synonyms

Amylumpregelificatum; compressible starch; C*PharmGel; Instastarch; Lycatab C; Lycatab PGS; Merigel; National 78-1551; Pharma-Gel; Prejel; Sepistab ST200; Spress B820; Starch 1500 G; Tablitz; Unipure LD; Unipure WG220.

Chemical Name and CAS Registry Number

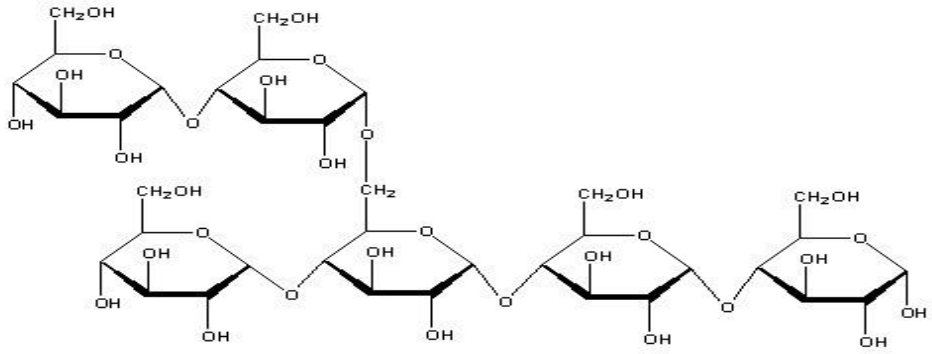
Pregelatinized starch [9005-25-8]

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n$ where n = 300–1000.

Pregelatinized starch is a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules. Both fully and partially pregelatinized grades are commercially available. Partial pregelatinization renders the starch flowable and directly compressible. Full pregelatinization produces a cold-water soluble starch that can be used as a wet granulation binder. Typically, pregelatinized starch contains 5% of free amylose, 15% of free amylopectin, and 80% unmodified starch. The USP32–NF27 does not specify the botanical origin of the original starch, but the PhEur 6.3 specifies that pregelatinized starch is obtained from maize (corn), potato, or rice starch. See also Starch and Section 13. Normally the fully pregelatinized starch contains 20–30% amylose and the rest amylopectin, which is about the same ratio (1 : 3) as for the partially pregelatinized form. There are ways to increase the amylose portion.

Structural Formula



Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tabletnbinder.

Applications in Pharmaceutical Formulation or Technology

Partially pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,anddisintegrant. In comparison to starch, partially pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry compression or direct compression processe. In such processes, pregelatinized starch is self-lubricating.

Stability and Storage Conditions

Pregelatinized starch is a stable but hygroscopic material, which should be stored in a well-closed container in a cool, dry place.

Safety

Pregelatinized starch and starch are widely used in oral solid-dosage formulations. Pregelatinized starch is generally regarded as a nontoxic and nonirritant excipient. However, oral consumption of large amounts of pregelatinized starch may be harmful.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and a dust mask are recommended. Excessive dust generation should be avoided to minimize the risks of explosions.

Regulatory Status

Included in the FDA Inactive Ingredients Database (oral capsules, suspensions, and tablets; vaginal preparations). Included in nonparenteral medicines licensed in the UK.

Related Substances

Corn starch and pregelatinized starch; starch; starch, sterilizablemaize.

Applications in Pharmaceutical Formulation or Technology

Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent,anddisintegrant.In comparison to starch, grades of pregelatinized starch may be produced with enhanced flow and compression characteristics such that the pregelatinized material may be used as a tablet binder in dry-compression or direct compression processes. In such processes, pregelatinized starch is self-lubricating. However, when it is used with other excipients it may be necessary to add a lubricant to a formulation.

Although magnesium stearate 0.25 w/w is commonly used for this purpose, concentrations greater than this may have adverse effects on tablet strength and dissolution.

Table-3 Uses of pregelatinized starch.

Use	Concentration (%)
Diluent (hard gelatin capsules)	5–75
Tablet binder (direct compression)	5–20
Tablet binder (wet granulation)	5–10
Tablet disintegrant	5–10

6.2 HYDROXYPROPYL CELLULOSE, LOW-SUBSTITUTED[36]

Nonproprietary Names

JP: Low Substituted Hydroxypropylcellulose

USP-NF: Low-Substituted Hydroxypropyl Cellulose

Synonyms

Cellulose, 2-hydroxypropyl ether; 2-hydroxypropyl ether (lowsubstituted) cellulose; hyprolose, low-substituted; L-HPC; oxypropylated cellulose.

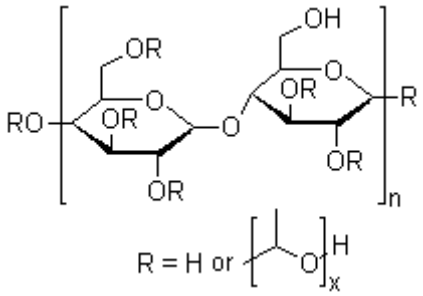
Chemical Name and CAS Registry Number

Cellulose, 2-hydroxypropyl ether (low-substituted) [9004-64-2]

Empirical Formula and Molecular Weight

$C_{36}H_{70}O_{19}$ and 576.762

Structural Formula



Functional Category

Tablet and capsule disintegrant; tablet binder.

Applications in Pharmaceutical Formulation or Technology

Low-substituted hydroxypropyl cellulose is widely used in oral solid-dosage forms. It is primarily used as a disintegrant, and as a binder for tablets and granules in wet or dry granulation. It has been used in the preparation of rapidly disintegrating tablets produced by direct compression methods. In addition, low substitutedhydroxypropyl cellulose has been used as a binder/ disintegrant included in the powder layering

process on spherical cores and to prepare pellets by extrusion/spheronization. A low particle size and high hydroxypropyl content is recommended to produce round spheres and rapid dissolution.

The typical content of low-substituted hydroxypropyl cellulose in a formulation is approximately 5–50%.

Description

Low-substituted hydroxypropyl cellulose occurs as a white to yellowish white powder or granules. It is odourless or has a slight, characteristic odor, and it is tasteless.

Solubility

Completely insoluble in water, and alcohol. Dissolves in 10% NaOH solution to give a viscous solution.Swells rapidly in water.

Physical Characteristics

PH (slurry): 5.0 –7.5

Loss on Drying: £ 5.0%

Table-4 HPC Characteristics

Product	Average Particle size (microns)	Hydroxypropyl content	Bulk Density (g/cc)
LH-11	50	Medium	0.34
LH-21	40	Medium	0.40
LH-31	25	Medium	0.30
LH-22	40	Low	0.37
LH-32	25	Low	0.21
LH-20	40	High	0.36
LH-30	25	High	0.25

Stability and Storage Conditions

Low-substituted hydroxypropyl cellulose is a stable, though hygroscopic, material. The powder should be stored in a well closed container.

Incompatibilities

Alkaline substances may interact. If a tablet formulation contains such a material, the disintegration time may be extended after storage.

Method of Manufacture

Low-substituted hydroxypropyl cellulose is manufactured by reacting alkaline cellulose with propylene oxide at elevated temperature. Following the reaction, the product is recrystallized by neutralization, washed, and milled.

Safety

Low-substituted hydroxypropyl cellulose is generally regarded as a nontoxic and non-irritant material. Animal toxicity studies showed no adverse effects in rats fed orally 6 g/kg/day over 6 months. No teratogenicity effects were noted in rabbits and rats fed 5 g/kg/day.(8–11) LD50 (rat, oral): >15 g/kg(8)

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be avoided to minimize the risk of explosions.

Regulatory Status

Included in the FDA Inactive Ingredients Database (oral capsules, tablets, pellets). Approved for use in pharmaceuticals in Europe,Japan, USA, and other countries. Included in the Canadian List of Acceptable Non-medicinal Ingredients.

Related Substances

Hydroxyethylmethyl cellulose; hydroxypropyl cellulose; methylcellulose.

Applications

Table-5 HPCLH-11 Applications

Disintegrant	Wet granulated and directly compressed tablets. Types with a larger average particle size and higher hydroxypropyl content show higher degree of swelling.
Binder	Direct compression. LH-22 provides greater binding while retaining disintegration properties. Binder levels are in the 25% range. LH-11 is useful to prevent capping.

6.3LYCATABC (pregelatinized starch)[36]

Nonproprietary Names

BP: Maize starch Potato starch Rice Starch Tapioca Starch Wheat Starch

JP: Corn Starch Potato Starch Rice Starch Wheat Starch

PhEur: Maize Starch Pea Starch Potato Starch Rice Starch Wheat Starch

USP-NF: Corn Starch Potato Starch Tapioca Starch Wheat Starch

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)n$ where n = 300–1000.

Particle size

Mean particle size: 100 µm, Low dust content

Properties

- Free flowing powder
- High Density
- Dispersible and partially soluble in cold water
- High powder cohesion
- Compatible with gelatin

Applications

- Filler disintegrant for hard gelatin capsules
- Binder disintegrant for direct compression
- Flow aid in powder blends

Functional Category

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

Description

Starch occurs as an odorless and tasteless, fine, white to off-white powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

Stability and Storage Conditions

Dry starch is stable if protected from high humidity. Starch is considered to be chemically and microbiologically inert under normal storage conditions. Starch solutions or pastes are physically

unstable and are readily metabolized by microorganisms; they should therefore be freshly prepared when used for wet granulation. Starch should be stored in an airtight container in a cool, dry place.

Incompatibilities

Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

Method of Manufacture

Starch is extracted from plant sources with specific processes according to the botanical origin. Typical production steps are steeping (corn), wet milling (corn, potato), dry milling (wheat), or sieving and physical separation with hydro cyclones. The last production step is usually a centrifugal separation from the starch slurry followed by drying with hot air. The starch separation process may use sulfur dioxide or peroxides as a processing aid, improving the separation process and the microbial quality of the final product.

Safety

Starch is an edible food substance, considered a food ingredient and not a food additive. It is regarded as an essentially nontoxic andnonirritant material. Starch is therefore widely used as anexcipient in pharmaceutical formulations.

6.4.SodiumStearyl Fumarate[36]

Nonproprietary Names

BP: Sodium Stearyl Fumarate

PhEur: Sodium Stearyl Fumarate

USP-NF: Sodium Stearyl Fumarate

Synonyms

Fumaric acid, octadecyl ester, sodium salt; natriistearylisfumaras; Pruv; sodium monostearyl fumarate.

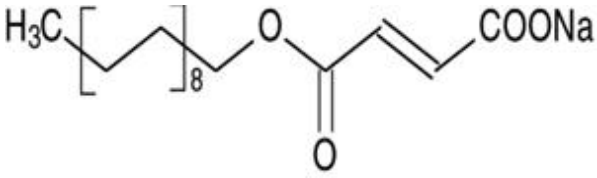
Chemical Name and CAS Registry Number

2-Butenedioic acimd,onooctadecyl ester, sodium salt [4070-80-8]

Empirical Formula and Molecular Weight

C22H39NaO4 and 390.5

Structural Formula



Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

Sodium stearyl fumarate is used as a lubricant in capsule and tablet formulations at 0.5–2.0% w/w concentration.(1–9) It is also used in certain food applications;

Description

Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.

Typical Properties

Acidity/alkalinity pH = 8.3 for a 5% w/v aqueous solution at908C.
Density 1.107 g/cm3
Density (bulk) 0.2–0.35 g/cm3
Density (tapped) 0.3–0.5 g/cm3
Specific surface area 1.2–2.0m2/g

Stability and Storage Conditions

At ambient temperature, sodium stearyl fumarate is stable for up to3 years when stored in amber glass bottles with polyethylene screw caps.

The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Sodium stearyl fumarate is reported to be incompatible with chlorhexidine acetate.

Method of Manufacture

Stearyl alcohol is reacted with maleic anhydride. The product of this reaction then undergoes an isomerization step followed by salt formation to produce sodium stearyl fumarate.

Safety

Sodium stearyl fumarate is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and non-irritant material. Metabolic studies of sodium stearyl fumarate in the rat and dog indicated that approximately 80% was absorbed and 35% wasrapidly metabolized. The fraction absorbed was hydrolyzed to stearyl alcohol and fumaric acid, with the stearyl alcohol further oxidized to stearic acid. In the dog,

sodium stearyl fumarate that was not absorbed was excreted unchanged in the feces within 24hours.

Stearyl alcohol and stearic acid are naturally occurring constituents in various food products, while fumaric acid is a normal constituent of body tissue. Stearates and stearyl citrate have been reviewed by the WHO and an acceptable daily intake for stearyl citrate has been set at up to 50 mg/kg body-weight. The establishment of an acceptable daily intake for stearates and fumaric acid was thought unnecessary.

Disodium fumarate has been reported to have a toxicity not greatly exceeding that of sodium chlorid

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Sodium stearyl fumarate should be handled in a well-ventilated environment; eye protection is recommended.

Regulatory Status

GRAS listed. Permitted by the FDA for direct addition to food for human consumption as a conditioning or stabilizing agent in various bakery products, flour-thickened foods, dehydrated potatoes, and processed cereals up to 0.2–1.0% by weight of the food. Included in nonparenteral medicines licensed in the UK.Included in the FDA Inactive Ingredients Database (oral capsules and tablets).Included in the Canadian List of Acceptable Non-medicinal Ingredients.

7.INNOVATOR PRODUCT CHARACTERIZATION

Generic name : Emtricitabine and Tenofovir disoproxil fumarate tablets

Brand name **:**TRUVADA

Manufactured By **:**Gilead Sciences Limited

Storage condition **:**Store at 15–30 °C (59–86 °F).

Dosage Form **:** Tablet

Strength **:** 200/300mg

Description **:**TRUVADA tablets are blue, capsule-shaped, film-coated, debossed with "GILEAD" on one side and with "701" on the other side

Pack details **:**TRUVADA tablets are packed in HDPE bottle containing silica gel desiccant with a child resistant cap containing an aluminium foil inner seal.

Tablet weight **:** Avg.Weight:1030mg

Uncoated/coated **:** Coated (Film coating)

Thickness (mm) **:** 6.48-6.86

Hardness (k/cm^2) **:** 26.5-27.5

Disintegration time **:** 11 min 30 sec

Figure-4 Innovator Product

8. MATERIALS AND METHODS

Table-6 List of materials

Name of Drug/Excipients	Brand Name / Grade	Source
Emtricitabine	USP	Arch Pharmalabs Ltd.
Tenofovir disoproxil fumarate	USP	Arch Pharmalabs Ltd.
Microcrystalline Cellulose pH 102	USP	Vijilakpharma
Di Calcium Phosphate	USP	Vijilakpharma
Pregelatinized starch	Lycotab-c	Signet Chemical Corporation Pvt Ltd.
Hydroxy Propyl Cellulose LH-II	USP	Colorcon Asia Pvt Ltd
Sodium Steryl Fumarate	USP	Amisti Drugs Ltd
Glycerol Bentoate	USP	Signet Chemical Corporation Pvt Ltd.
Starch 1500	USP	Amisti Drugs Ltd
Opadry II Blue (Y-30-1070)	-	Colorcon Asia Pvt Ltd.

Table-7 List of equipments

NAME OF INSTRUMENT	MODEL AND MANUFACTURER
Digital Balance	Mettler Toledo PR203
Rapid Mix Granulator	RMG5 Anchor Mark Pvt Ltd
Fluid bed dryer	UmangPharmatech Pvt Ltd,Mumbai
Moisture Analyzer	Advance Research Instruments
Tap Density Tester USP	Electrolab,Mumbai
Tabletting Machine-27Stn	Rimek,Ahmedabad
Vernier Calliper	Mitutoyo,China
Hardness Tester	SQC & Inspection instruments,Mumbai
Disintegration Test Apparatus USP	Tab machines
Friabilator USP	Veegoinstruments,Mumbai
Mechanical Stirrer	Neomachine,Mumbai
Auto coater	Neocota,Mumbai
Dissolution Apparatus USP XXII	ElectroLab,Ahmedabad
HPLC with Autosampler	Waters ,USA
pH meter	Metro HM ,Switzerland

Table-8 APICharacterization -Emtricitabine

S.No.	Test	Specification
01	Description	White to off white powder
02	Solubility	Freely Soluble in dimethyl formamide and soluble in methanol.
03	Water content(%w/w)	Should be not more than 1.0 %w/w
04	Melting range(^{o} c)	114 to 118
05	Residue on ignition(%w/w)	Should be not more than 0.2 %w/w
06	Heavy metals(ppm)	Should be not more than 20%w/w
07	Fumaric acid content by potentiometry (%w/w) (on anhydrous basis)	17.5 – 19
08	S-Isomer content by chiral HPLC (%area)	Should be not more than 1 %w/w

Table-9 Related compounds of Emtricitabine BY HPLC

01	**Related compounds by HPLC**
A)	Method -1(%w/w)
	a) Sulfoxide-I impurity Should be not more than 0.2%
	b) Sulfoxide-II impurity Should be not more than 0.2%
	c) 5 Flourocystine impurity Should be not more than 0.2%
	d) Mono ester impurity Should be not more than 0.3%
	e) Adenine impurity Should be not more than 0.2%
	f) Other impurities Should be not more than 1.0%
	h) Total impurities Should be not more than 2.5%

Table-10 API Characterization - Tenofovir disoproxil fumarate

S.No.	Test	Specification
01	Description	White to off white powder
02	Solubility	Freely Soluble in dimethyl formamide and soluble in methanol.
03	Water content(%w/w)	Should be not more than 1.0 %w/w
04	Melting range(^{o} c)	114 to 118
05	Residue on ignition(%w/w)	Should be not more than 0.2 %w/w
06	Heavy metals(ppm)	Should be not more than 20%w/w
07	Fumaric acid content by potentiometry (%w/w) (on anhydrous basis)	17.5 – 19

Table-11 Related compounds of Tenofovir Disoproxil Fumarate BY HPLC

01	**Related compounds by HPLC**
A)	Method -1(%w/w)
	a) Sulfoxide-I impurity Should be not more than 0.2%
	b)Sulfoxide-II impurity Should be not more than 0.2%
	c) 5 Flourocystine impurity Should be not more than 0.2%
	d) Mono ester impurity Should be not more than 1%
	e) Adenine impurity Should be not more than 0.2%
	f) Other impurities Should be not more than 1.0%
	h) Total impurities Should be not more than 2.5%

8.1 PREFORMULATION STUDIES

8.1.1 Compatibility Studies[37,38]

A Compatibility study focuses on a binary mixture of drug substance and some selected excipients in a fixed ratio with or without added moisture.The mixture is stored at elevated temperatures of 40°c 75%RH and 55°C 60%RH in capped vials. The interaction between the active drug and excipients is determined by HPLC. The results were given in table 23,24,25,26.

Procedure

1. Drug and Excipients mixture shall be prepared based on the information from Physician Desk Reference (PDR).
2. The Drugs and Excipients individually and in combination shall be subjected for accelerated study conditions along with control samples and study at fixed intervals
3. The recommended drug- excipients ratios for solid dosage forms are tabulated below

Table-12 Drug excipient ratios for solid dosage forms

Name of Excipient	Quantity of Drug in mg					
	< 5 mg	**5 ≤ 10mg**	**10 ≤ 50mg**	**50 ≤ 200mg**	**200 ≤ 500mg**	**≥500 mg**
Fillers & Diluents	1:40	1:20	1:10	1:5	1:2	1:1
Disintegrants / Polymers	1:10	1:5	1:1	1:1	1:0.5	1:0.25
Binders	1:10	1:5	1:1	1:0.5	1:0.25	1:0.1
Lubricants	1:0.5	1:0.5	1:0.25	1:0.1	1:0.05	1:0.05
Coating agents	1:5	1:5	1:1	1:0.5	1:0.25	1:0.1
Colours / Sweetners	1:0.05	1:0.05	1:0.05	1:0.05	1:0.05	1:0.05

Table-13Study conditions and parameters to be analysed

Name of the drug/excipients	Ratio	Test Parameters		
		Initial	Period-14 & 28 Days	
			55°C/60%RH	40°C/75%RH
Emtricitabine (200mg)	-	RS&A	RS & A	RS & A
Tenofovir disoproxil fumarate(300mg)	-	RS&A	RS & A	RS & A
Emtricitabine+ Tenofovir disoproxil fumarate+microcrystalline cellulose PH 102	1:2	RS&A	RS & A	RS & A
Emtricitabine+ Tenofovir disoproxil fumarate+ Di Calcium Phosphate	1:2	RS&A	RS & A	RS & A
Emtricitabine+ Tenofovir disoproxil fumarate+ Starch1500	1:1	RS&A	RS & A	RS & A
Emtricitabine+ Tenofovir disoproxil fumarate+ Lycatab-c	1:1	RS&A	RS & A	RS & A
Emtricitabine+ Tenofovir disoproxil fumarate+ Hydroxy Propyl Cellulose LH-11	1:1	RS&A	RS & A	RS & A
Emtricitabine+ Tenofovir disoproxil fumarate+ Sodium Steryl Fumarate	1: 0.1	RS&A	RS & A	RS & A

Emtricitabine+ Tenofovir disoproxil fumarate+ Glycerol Bentoate	1:0.1	RS&A	RS & A	RS & A
Emtricitabine+ Tenofovir disoproxil fumarate+coating agent(OpadryBlue-II)	1:0.1	RS&A	RS& A	RS & A
Placebo+Emtricitabine	1:1	RS&A	RS & A	RS & A
Placebo+tenofovir disoproxil fumarate	1:1	RS&A	RS & A	RS & A
Placebo+emtricitabine+tenofovir disoproxil fumarate	1:1	RS&A	RS & A	RS & A

Where, API = Active Pharmaceutical Ingredient (Clopidogrel Bisulphate),RS = Related substances, A = Appearance.

8.1.2 Angle of repose[39,40,41]

Angle of Repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.The angle of repose is determined by funnel method.The funnel is fixed at a particular height (2.5 cm)on a burette stand.The powder sample was passed through the funnel allowing it to form a pile.No more granules are added as the pile touches the tip of the funnel.This region is encircled to measure radius.The same procedure is done for triplicate,the average value is taken.The values are given in table28The angle of repose is calculated by using equation.

$$\text{Angle of Repose } (\theta) = \tan^{-1}(h/r)$$

Where, h = height of pile

r = radius of the base of the pile

θ = angle of repose

Table-14 Angle of repose and corresponding flow properties

Angle of Repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

8.1.3 Bulk density determination[39,40,41]

Weighed quantity of the powder (W) is taken in a graduated measuring cylinder and volume (V_0) is measured the reading were shown in table 28. Bulk density is calculated using the formula.

Bulk density (BD) = Weight of the powder/ Volume of powder

8.1.4 Tapped density determination[39,40,41]

Weighed quantity of powder(W) is taken in a graduated cylinder and the volume is measured. The graduated cylinder was fixed in the 'Tapped Densitometer' and tapped for 500, 750 and 1250 times until the difference in the volume after consecutive tappings was less than 2%. The final reading was denoted by (V_f). The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.The reading were shown in table 28.

Tapped density (TD) = W/V_f g/ml

8.1.5 Carr's index[39,40,41]

Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics.

Table-15 Carr's index and corresponding flow properties

Carr's Index (%)	Flow
5-15	Excellent
16-18	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Carr's index was calculated by using the formula:

$$\textbf{Carr's Index} = \frac{\textbf{(Tapped Density – Bulk Density)}}{\textbf{Tapped Density}} \times 100$$

8.1.6 Hausnerratio[39,40,41]

Hausner ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density. The relationship between Hauser's ratio and flow property

Table-16Hausner ratio and corresponding flow properties

Hausner Ratio	Property
0-1.2	Free flowing
1.2-1.6	Cohesive Powder

Hausner ratio was calculated by using the formula.

$$\text{Hausner Ratio} = \text{Tapped density / Bulk density}$$

$$\textbf{Hausner Ratio} = \frac{V_0}{V_f}$$

Where, V_0= Initial volume

V_f = Final volume

8.2 SELECTION OF EXCIPIENTS

The following are the excipients selected from the compatibility studies.

- Emtricitabine
- Tenofovir disoproxil fumarate
- DiCalcium Phosphate
- Starch 1500
- Pregelatinized Starch(lycotab-c)
- Hydro Propoxy Cellulose(HPC) LH-11
- Sodium Steryl Fumarate
- Opadry Blue II

8.3PREPARATION OF STANDARD GRAPH OF TENOFOVIR AND EMTRICITABINE

Standard Stock Solution

Tenofovir and Emtricitabine were weighed separately (100 mg) and dissolved in buffer and made up to 100ml in volumetric flasks to get a concentration of 1000μg/ml.

Calibration Graph

The standard stock solution of TDF was diluted to get a concentration ranging 5-30 μg/ml. The absorbance of the resulting solutions were measured at 257 nm. Similar procedure was followed for EMB and absorbance measured at 280 nm by using high pressure liquid chromatography(HPLC). It was found that the TDF and EMB showed good linearity at concentrations ranging 5-30 μg/ml. the readings were showed in table 27 and the fig 6 & 7.

8.4 working formulae

Table 17: Working Formulae

S.No.	Ingredients	Rationale	Quantity for Single Tablet									
			F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Emtricitabine	API	200	200	200	200	200	200	200	200	200	200
2.	Tenofovir disoproxil fumarate	API	300	300	300	300	300	300	300	300	300	300
3.	DiCalcium Phosphate	Diluent	390	390	390	390	390	390	340	340	410	370
4.	Starch 1500	Disintegrant	60	60	60	60	80	----	----	----	---	---
5.	Lycatab c (pregalatinized starch)	Disintegrant	----	----	----	----	---	60	80	----	----	----
6.	Hydroxy Propyl Cellulose(HPC)LH-11	Disintegrant	----	----	----	----	----	---	----	60	50	80
7.	Water	Vehicle	----	----	Q.s	----	----	----	----	----	----	----
8.	Iso Propyl Alcohol+ Water(80:20)	Vehicle	----	----	----	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
9.	Starch 1500	Disintegrant	40	40	40	40	40	----	----	----	---	---
10.	Lycatab c	Disintegrant	----	----	----	----	---	40	40	----	----	----
11.	Hydroxy Propyl Cellulose(HPC)LH-11	Disintegrant	----	----	----	----	----	---	----	40	30	40
12.	Sodium Steryl Fumarate	Lubricant	10	10	10	10	10	10	10	10	10	10
13.	Opadry Blue II	Film former	30	30	30	30	30	30	30	30	30	30

8.5 METHOD OF PREPARATIONS

Process Validation

DIRECT COMPREESION(F1)

Objective

FormualtionFI (table17) of Emtricitabine and Tenofovir disoproxil fumarate tablets by Prepared Direct compression method.

Procedure:(Direct Compression)

Dispensing of API + Excipients

↓

D.C.P + Starch1500 Shifted through 40#

↓

Emtricitabine + Tenofovir Shifted through 24#

↓ **Lubricated**

Sodium steryl fumarate + Starch1500

↓

Direct Compression

(19×8.5 Punch Capsule shape)

↓

Coating

(Opadry solution (15%))

DRY GRANULATION(F2)

Objective

To take a trial batch of Emtricitabine and Tenofovir disoproxil fumarate tablets by Dry Granulation Method.

Procedure

Step I

Dispensing

The dispensing of active pharmaceutical ingredient and Excipients was carried out in dispensing booth as per manufacturing formula.

Step II

Emtricitabine and Tenofovir disoproxil fumarate DiCalcium Phosphate and Starch1500 were mixed sifted through #30 meshes.

Step II

Slugs were Prepared by punching of the above mixture

Step IV

Theprepared Slugs were crushed by using Rollercompression and the granules were pass through 18# mesh.

Step V

The dry granules were lubricated with Sodium Steryl Fumarate and starch1500 which were previously passed through 30#mesh.

Step VI

The lubricated powder was compressed into tablets by using 19*8.5 punch (capsule shape)

Step VII

The prepared tablets were coated by using opadry blue solution.

WET GRANULATION (F3) (Only with Water)

Objective

The formulation F3 of Emtricitabine and Tenofovir disoproxil fumarate tablets were prepared by wet- granulation method by using water as vehicle.

Procedure

Step I

Dispensing

The dispensing of active pharmaceutical ingredient and excipients was carried out in dispensing booth as per manufacturing formula.

Step II

Emtricitabine and Tenofovir disoproxil fumarate, DiCalcium Phosphate and Starch1500 were mixed sifted through #30 mesh and the granules were prepared with the vehicle and pass through 12# mesh.

Step III

The granules were dried in tray dryer at 55^0C. the dry granules were pass through 18# mesh and lubricated with sodium sterylrumarate and starch1500

Step IV

The lubricated powder was compressed into tablets by using 19*8.5 punch (capsule shape)

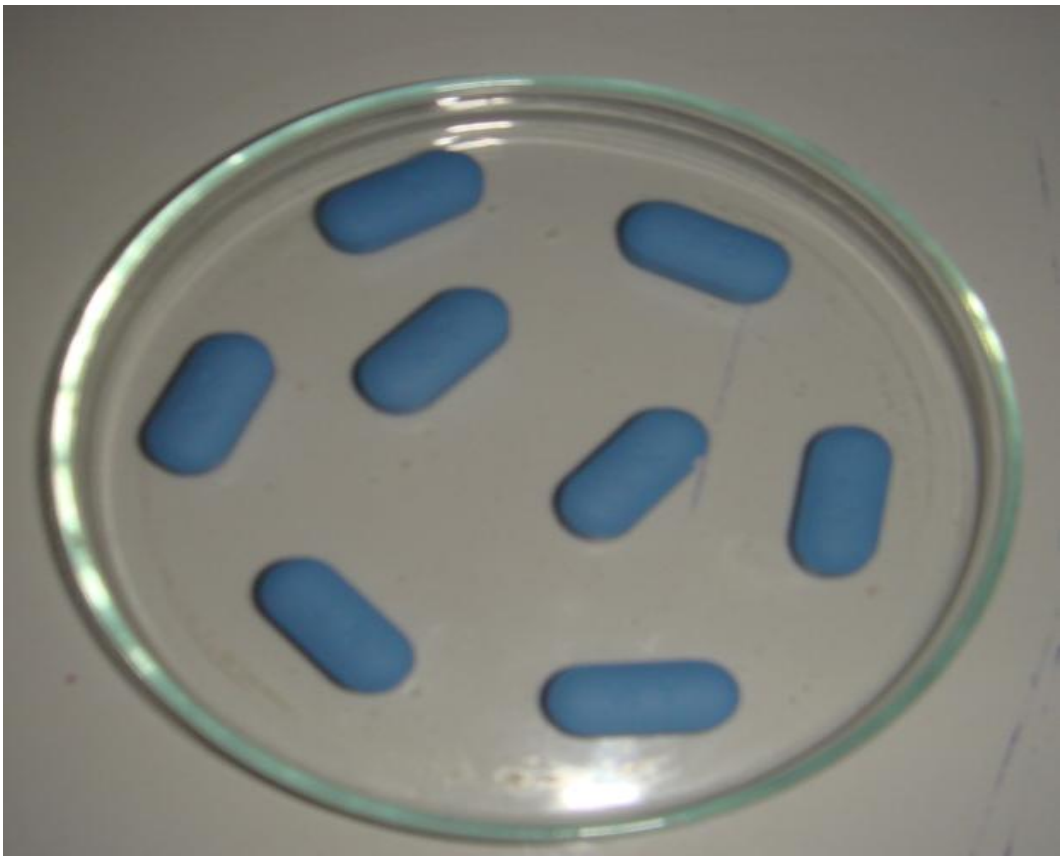
StepV

Then finally tablets were coated by using the Opadry blue solution.

WET GRANULATION (F4) Procedure-II

Due to presence of impurities found in the wet granulation prepared with water as vehicle. The vehicle was changed to mixture of IPA and Water (80:20). The remaining procedure was same as above. F5- F10 the same procedure of F4 was followed by changing the disintegrants by changing the concentration(Starch1500, Lycatab C and HPCLH-11)

Figure-5 Prepared Emtricitabine and Tenofovir disoproxil fumarate immediate release tablets.



8.6EVALUATION OF TABLETS

Evaluation of tablets

Determination of physicochemical parameters of final tablets

1. Drug content uniformity
2. Weight variation
3. Thickness
4. Hardness
5. Friability
6. Disintegration Test
7. Dissolution studies
8. chromatographic method (HPLC)
9. Stability studies

8.6.1 Drugcontentuniformity[42]

Although the specifications for assay results differ from product to product, generally the expected range for individual active ingredient is to be within 90%–110% of the labeled amount.

Instrument

HPLC equipped with UV detector and data handling system.

Apparatus

Analytical balance,Volumetric flasks,Pipettes,0.45µ membrane filters.

Chemicals and reagents

Potassium dihydrogen phosphate	-GR grade
Ortho-phosphoric acid	-HPLC grade
Purified water-Milli	-Q grade
Acetonitrile	-HPLC grade

Emtricitabine working standard

Tenofovir disoproxil fumarate working standard

Chromatographic conditions

Column:Purosphere star –RP18 , 150 * 4.6 mm,5µm

Flowrate :1.0 ml/min

Wavelength :UV-254 nm

Column temperature :30^{o}c

Injection volume :20µl

Run time :12 min.

Preparations

Buffer preparation

Accurately weigh and transfer about 4.4 gm of Potassium dihydrogen phosphate into 1000 ml of purified water.Adjust the p^{H} of solution to 3.0 with dilute Ortho-phosphoric acid.

Mobile phase –A preparation

Prepare a filtered and degassed mixture of buffer and Acetonitrile in ratio of 970 :30 v/v respectively.

Mobile phase –B preparation

Prepare a filtered and degassed Acetonitrile –HPLC grade ..4. Diluent preparation: Mix buffer and Acetonitrile in ratio of 60:40 v/v respectively.

Emtricitabine and Tenofovir disoproxil fumarate standard preparation

Accurately weigh and transfer about 20mg of Emtricitabine working standard and 30mg of Tenofovir working standard into a 250 ml volumetric flask.

Add about 180ml of diluents and sonicate to dissolve.Cool the solution to room temperature and dilute to volume with diluents(0.08 mg/ml of Emtricitabine and 0.12 mg/ml of Tenofovir).Trensfer 2ml of above solution into a 200ml volumetric flask ,mix well and dilute to volume with Mobile phase –A and mix.

Sample preparation

Weigh and finely powder not fewer than 20 tablets..Transfer an accurately weighed portion of the powder equivalent to 200 mg of emtricitabine into 250ml volumetric flask.Add 180ml of diluents.Shake for 10min with rotating shaker and sonicate for 30min with occasional shakings.Cool the solution to room temperature and dilute to volume with diluents and mix.Centrifuge the solution to 3000 rpm for 10 min.Transfer 1ml of above centrifuged solution into 100ml volumetric flask and dilute with Mobile phase –A.

System suitability

Chromatograph the standard preparation (six replicate injections),measure the peak area response for the analyte peak and evaluate the system suitability parameters as directed.

Acceptance criteria

1.%RSD for replication of peak area response due to emtricitabine and tenofovir peak from the standard preparation should be not more than 2.0

2.The tailing factor for emtricitabine and tenofovir peak should be not more than 2.0

3.The number of theoretical plates for emtricitabine and tenofovir peak should be not less than 2000.

Procedure

Seperately inject equal volumes(about 20µl)of the water as blank,standard preparation and sample preparation into chromatograph and record the chromatograms and measure the peak area response for analytepeak.Calculate the percentage content of Emtricitabine and Tenofovir disoproxil fumarate tablets taken by formula. The chromatograms were shown in fig 8,9,10,11&12.

Percentage content of Emtricitabine / Tenofovir disoproxil fumarate

= TA / SA * SW / 250 * 2/20 * 250/TW * 100/1 * P/100 * AVG WT/ LA * 100

Where,

TA = Peak area response due to Emtricitabine / Tenofovir disoproxil fumarate fromsamplepreparation

SA= Peak area response due to Emtricitabine / Tenofovir disoproxil fumarate from standard preparation

SW=Weight of Emtricitabine / Tenofovir disoproxil fumarate working standard taken in mg.

TW=Weight of sample taken in mg.

P=Purity of Emtricitabine / Tenofovir disoproxil fumarate working standard taken on ,as is basis.

AVG WT=Average weight of tablets.

LA=Labelled amount of Emtricitabine / Tenofovir disoproxil fumarate.

8.6.2WEIGHT VARIATION TEST[39,43]

Twenty (20) tablets from each batch were individually weighed. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight

Weight Variation limits as per USP and the values were showed in the table-30.

Table -18 :Weight Variation that has be presented solid dosage form

Average weight in mg	% ± deviation allowed
130 or less	10
130-324	7.5
More than 324	5

8.6.3THICKNESS TEST[39,43]

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Vernier Caliper's. The average thickness and standard deviation were reported in table-30 and fig 13.

8.6.4HARDNESS TEST[39,43]

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness, and the standard deviation was reported and the values were shown in the table-30 and fig -14.

8.6.5FRIABILITY TEST[39,43]

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche friablator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets. The values were shown in the table-30.

%Friability= Initial wt- Final wt / Initial wt x100

8.6.6DISINTEGRATION TEST[44,45]

The test was carried out on 6 tablets using Tablet disintegration tester. Distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in seconds taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured and values shown in the table-30 and fig -15.

Table-19ThePharmacopoeial specifications for disintegration testing.

Tablet Type	Time limit and Specifications
BP	
Uncoated	<15min
Coated	
Film	<30min
Sugar	<60min, repeat in 0.1MHCl
Gastro resistant, enteric	>120min in 0.1MHCl <60min in pH 6.8(Phosphate)
Effervescent	<5min in 200mL, water, 20°C
Soluble	<3min
Dispersible	<3min, 2 tablets in 100mL water dispersed, passed 7150 um
USP	
Uncoated	<15min
Plain coated	<30 min
Enteric coated	Intact for 60min in simulated gastric fluid, disintegrated in simulated intestinal fluid<monograph time
Buccal	<4hours

8.6.7DISSOLUTION TEST [37,46]

Dissolution conditions

Dissolution studies were performed in a calibrated 8 station dissolution test apparatus equipped with paddles (USP apparatus II method) employing 900 ml of 0.01 N HCL as a medium. The paddles were operated at 50 rpm and temperature was maintained at 37 ± 0.5 ºC throughout the experiment. 5 ml samples were withdrawn at 5,10, 15, 30 & 45 min of time periods as given by FDA dissolution

data base. Equal volume of dissolution medium was replaced to maintain the constant volume throughout the experiment. Samples withdrawn and diluted with same medium and the amount of the drug dissolved was estimated UV spectrophotometer at 254 nm. Dissolution profiles are shown in table 33,34 and fig 18 &19.

HPLC method

Instrument

HPLC equipped with UV detector and data handling system.

Apparatus

Analytical balance,Volumetric flasks , Pipettes ,0.45µ membrane filters , syringes ,dissolution apparatus .

Chromatographic conditions

Column:Purosphere star –RP18 , 150 * 4.6 mm,5µm

Flowrate :1.0 ml/min

Wavelength :UV-254 nm

Column temperature :30^{o}c

Injection volume :10µl

Run time :12 min.

Preparations

Mobile phase –A preparation

Prepare a filtered and degassed mixture of phosphate buffer pH 3.0 and Acetonitrile in ratio of 970 :30 v/v respectively.

Mobile phase –B preparation

Prepare a filtered and degassed Acetonitrile –HPLC grade.

Dissolution test

Emtricitabine and Tenofovir disoproxil fumarate standard preparation

Accurately weigh and transfer about 22.2mg of Emtricitabine working standard and 33.3mg of Tenofovir working standard into a 100 ml volumetric flask. Add about 60ml of diluents and sonicate todissolve.Cool the solution to room temperature and dilute to volume with dissolution medium .

Sample preparation

The dissolution of the tablets was performed by USP typeII paddle apparatus.

Place one tablet in each of six dissolution flask containing 900ml of dissolution medium -(0.01 N HCL) previously maintained at $37^{o}c \pm 0.5^{o}c$,taking care to exclude air bubbles from the surface of each dosage unit and immediately operate the apparatus for 45min.

5ml were withdraw at specified time interval(5,10,15,30,45) from zone midway between the surface of dissolution medium and top of rotating blade,not less than 1 cm from vessel wall and filter through 0.45 µ membrane filter and analyzed using HPLC at 254nm. The same amount of fresh buffer was replaced. The cumulative % drug release was plots against time for different formulations.

Percentage content of Emtricitabine / Tenofovir disoproxil fumarate

= TA / SA * SW / 100 * 900/1 * P/100 * 100/ LA

TA = Peak area response due to Emtricitabine / Tenofovir disoproxil fumarate fromsamplepreparation

SA= Peak area response due to Emtricitabine / Tenofovir disoproxil fumarate from standard preparation

SW=Weight of Emtricitabine / Tenofovir disoproxil fumarate working standard taken in mg.

P=Purity of Emtricitabine / Tenofovir disoproxil fumarate working standard taken on ,as is basis.

LA=Labelled amount of Emtricitabine / Tenofovir disoproxil fumarate.

8.6.8 DISSOLUTION PROFILE MODELING

Over recent year, the *In vitro* dissolution has been recognized as an important tool in drug development. *In vitro* dissolution has been recognized as an important parameter in quality control and under certain conditions, it can be used as a surrogate for the assessment of bio-equivalence or prediction of bioequivalence. Guidance recommends USP dissolution apparatus 1, 2, 3 or 4 for modified release dosage forms and generally this equipment is satisfactory. However, modifications of current dissolution equipment or completely new agitation, changing the media, and holding the dosage form in the media without interfering with the release mechanism require careful planning.

An appropriate drug release test is required to characterize the drug product and ensure batch to batch reproducibility and consistent pharmacological/biological activity and to evaluate scale up and post approval changes such as manufacturing site changes, component and composition changes. The release of drug from a sustained release formulation is controlled by various factors through different mechanism such as diffusion, erosion or osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems. In order to characterize the kinetics of drug release from dosage forms several model dependent methods are reported by various researchers.

The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modeling. Linear models include Zero order, Higuchi, Hixson – Crowell, Quadratic and Polynomials, where as the nonlinear models include First order, Weibull, KorsMeyer – Peppas, Logistic etc.

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and Reference dissolution profiles are as follows

- **Zero order kinetics**
- **First order kinetics**
- **Korsmeyer-Peppas model**
- **Higuchi model**

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$W_0 - W_t = K_0 t$$

Where, W_0 = the initial amount of drug in the pharmaceutical dosage form and W_t= the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First order kinetics

This type of model to analyze drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Where, Q_t =the amount of drug released in time t,

Q_0 = initial amount of drug in the solution and K_1 is the first order release rate constant.

In this way a graphical relationship between log percent drug remaining versus time to get the First order constant from the slope.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior, in such a way, that the amount of drug released by unit of time diminishes.

KorsmeyerPeppas model

Korsmeyer et al., (1983) developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$\mathbf{Q_t/Q_\alpha = K_k t^n}$$

Where ,K_k = a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent , indicative of the drug release mechanism. For matrix tablets , an n value of ~0.5 indicates diffusion – controlled mechanism while an n value of ~1.0 indicates erosion. If the value of n is 0.5, it indicates Fickian transport, a value of 0.5 >n> 1.0 non-Fickian transport combination of both erosion and diffusion controlled release. The values greater than one indicates the drug is releasing by the erosion of polymeric chain.

Table-20: **Showing drug mechanism based on release kinetics**

Release exponent (n)	**Drug transport mechanism**
0.5	Fickian diffusion
0.5<n<1.0	Anomalous transport
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

This type of analysis of release behavior is valuable is to the formulator for comparative purposes . The Release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

Higuchi Model

$$\mathbf{Q_t = K_H t^{1/2}}$$

Where, Q_t = the amount of drug released at time t and

K_H = the Higuchi release rate;

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus concentration indicates that the drug release follows strict Fickian diffusion.

For purpose of data treatment, the above equation is usually reduced to:

$$\mathbf{Q = Kt^{1/2}}$$

Therefore a plot of amount of drug released versus the square root of time should be linear if drug release from the matrix is diffusion controlled. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time. An important advantage of the above equations is its simplicity.

The order of release and mechanism of release for the optimized formulation were reported in table-36 & 38 and fig-20-27.

8.6.9STABILITY STUDIES[47,48,49,50]

The stability studies were carried out according to ICH to assess the drug formulation stability. Optimized FV formulation was sealed in aluminium packaging laminated with polyethylene. Sample were kept at 40 ^{0}C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics. The values were showed in the table-39.

9. RESULTS

Table-21API Characterization for Emtricitabine

Description	White powder
Solubility	Complies
Water content(%w/w)	0.5%w/w
Melting range(^{o} c)	114.8 to 116.5
Residue on ignition(%w/w)	0.1
Heavy metals(ppm)	Less than 20%w/w
Fumaric acid content by potentiometry (%w/w) (on anhydrous basis)	18.7
S-Isomer content by chiral HPLC (%area)	Below quantitation limit

Table-22API Characterization for Tenofovir disoproxilfumarate

Description	White powder
Solubility	Complies
Water content(%w/w)	0.5%w/w
Melting range(^{o} c)	114.8 to 116.5
Residue on ignition(%w/w)	0.1
Heavy metals(ppm)	Less than 20%w/w
Fumaric acid content by potentiometry (%w/w) (on anhydrous basis)	18.7

9.1 Drug-excipient compatibility Result

Table-23 Drug-excipient compatibility result(Initial for Emtricitabine and Tenofovir)

NAME OF THE DRUG/EXCIPIENT	RATIO	IMP A	IMP B	IMP C	IMP D	IMP E	IMP F	OTHER IMP	TOTAL IMP
Emtricitabine(ECB)	1	0.031	ND	0.220	ND	ND	ND	0.02	0.271
Tenofovir Disoproxil Fumarate(TDF)	1	ND	ND	ND	0.026	0.031	0.021	0.03	0.108
(ECB+TDF) + DicalciumPhosphate	1:2	0.050	ND	0.024	0.414	0.112	0.071	0.115	0.786
(ECB+TDF) + MCC PH102	1:2	0.052	ND	0.027	0.450	0.108	0.082	0.125	0.844
(ECB+TDF)+ Starch1500	**1:1**	0.060	ND	0.029	0.411	0,123	0.076	0.111	0.810
(ECB+TDF)+ Lycotab-c	**1:1**	0.048	ND	0.015	0.409	0.106	0.081	0.121	0.780
(ECB+TDF) + HPCLH-11	**1:1**	0.051	ND	0.016	0.411	0.124	0.061	0.110	0.773
(ECB+TDF) + Sodium Stearyl Fumarate(SSF)	**1:0.1**	0.047	ND	0.021	0.419	0.119	0.063	0.103	0.772
(ECB+TDF) + GlycerylBentonate	**1:0.1**	0.040	ND	0.012	0.436	0.121	0.062	0.108	0.779

Table-24 Drug-excipient compatibility result 14 Days (55°C/60%RH)

NAME OF THE DRUG/EXCIPIENT	RATIO	IMP A	IMP B	IMP C	IMP D	IMP E	IMP F	OTHER IMP	TOTAL IMP
Emtricitabine(ECB)	1	0.031	ND	0.022	ND	ND	ND	0.02	0.073
Tenofovir Disoproxil Fumarate(TDF)	1	ND	ND	ND	0.034	0.039	0.040	0.04	0.153
(ECB+TDF) + DicalciumPhosphate	1:2	0.051	ND	0.024	0.414	0.112	0.071	0.125	0.797
(ECB+TDF) + MCC PH102	1:2	0.069	ND	0.030	0.450	0.118	0.094	0.135	0.896
(ECB+TDF)+ Starch1500	**1:1**	0.076	ND	0.031	0.423	0,138	0.079	0.133	0.880
(ECB+TDF)+ Lycotab-c	**1:1**	0.054	ND	0.021	0.417	0.138	0.084	0.129	0.843
(ECB+TDF) + HPCLH-11	**1:1**	0.056	ND	0.019	0.414	0.142	0.076	0.129	0.836
(ECB+TDF) + Sodium Stearyl Fumarate(SSF)	**1:0.1**	0.048	ND	0.027	0.421	0.133	0.072	0.113	0.814
(ECB+TDF) + GlycerylBentonate	**1:0.1**	0.047	ND	0.021	2.123	0.130	0.079	0.120	2.520

Table-25Drug-excipient compatibility result 28 Days (40°C/75%RH)

NAME OF THE DRUG/EXCIPIENT	RATIO	IMP A	IMP B	IMP C	IMP D	IMP E	IMP F	OTHER IMP	TOTAL IMP
Emtricitabine(ECB)	1	0.031	ND	0.220	ND	ND	ND	0.02	0.271
Tenofovir Disoproxil Fumarate(TDF)	1	ND	ND	ND	0.026	0.031	0.021	0.03	0.108
(ECB+TDF) + DicalciumPhosphate	1:2	0.050	ND	0.024	0.414	0.112	0.071	0.115	0.786
(ECB+TDF) + MCC PH102	1:2	0.055	ND	0.029	1.300	0.110	0.089	0.131	1.714
(ECB+TDF)+ Starch1500	**1:1**	0.059	ND	0.025	0.421	0.146	0.083	0.139	0.873
(ECB+TDF)+ Lycotab-c	**1:1**	0.055	ND	0.016	0.419	0.134	0.081	0.127	0.832
(ECB+TDF) + HPCLH-11	**1:1**	0.054	ND	0.022	0.419	0.127	0.075	0.110	0.807
(ECB+TDF) + Sodium Stearyl Fumarate(SSF)	**1:0.1**	0.050	ND	0.029	0.425	0.128	0.079	0.111	0.822
(ECB+TDF) + GlycerylBentonate	**1:0.1**	0.049	ND	0.027	1.251	0.123	0.064	0.109	1.623

IMPURITIES:

EMTRICITABINE

IMP A-Sulfoxide I

IMP B-Sulfoxide II

IMP C-5 Flurocytosine

TENOFOVIR DISOPROXIL FUMARATE

IMP D-Monoester

IMP E-Adenine

IMP F-Isopropyl

ND **:** Not Detected.

ECB **:** Emtricitabine

TDF **:** Tenofovir Disoproxil Fumarate

HPCLH-11 **:** HydroxyPropyl Cellulose LH-II.

SSF **:** Sodium Steryl Fumarate.

MCC **:** Micro Crystalline Cellulose

Table-26 Drug-excipients compatibility Result by Appearance

NAME OF THE DRUG/EXCIPIENTS	RATIO	DESCRIPTION		
		INITIAL	14 Days (55°C/60%RH)	28 Days (40°C/75%RH)
Emtricitabine(ECB)	1	Off White	No Change	No Change
Tenofovir Disoproxil Fumarate(TDF)	1	Off White	No Change	No Change
(ECB+TDF) + DicalciumPhosphate	1:2	Off White	No Change	No Change
(ECB+TDF) + MCC PH102	1:2	Off White	No Change	No Change
(ECB+TDF)+ Starch1500	**1:1**	Off White	No Change	No Change
(ECB+TDF)+ Lycotab-c	**1:1**	Off White	No Change	No Change
(ECB+TDF) + HPCLH-11	**1:1**	Off White	No Change	No Change
(ECB+TDF) + Sodium Stearyl Fumarate(SSF)	**1:0.1**	Off White	No Change	No Change
(ECB+TDF) + GlycerylBentonate	**1:0.1**	Off White	No Change	No Change

9.2Calibration Curve of Emtricitabine and Tenofovitdisoproxilfumarate.

Table-27 Standard graph for Emtricitabine and Tenofovir

Concentration(ug/ml)	Emtricitabine Absorbance	Tenofovir Absorbance
5	0.11	0.096
10	0.212	0.186
15	0.32	0.287
20	0.425	0.374
25	0.534	0.475
30	0.623	0.564

Figure-6 Calibration curve for EMT

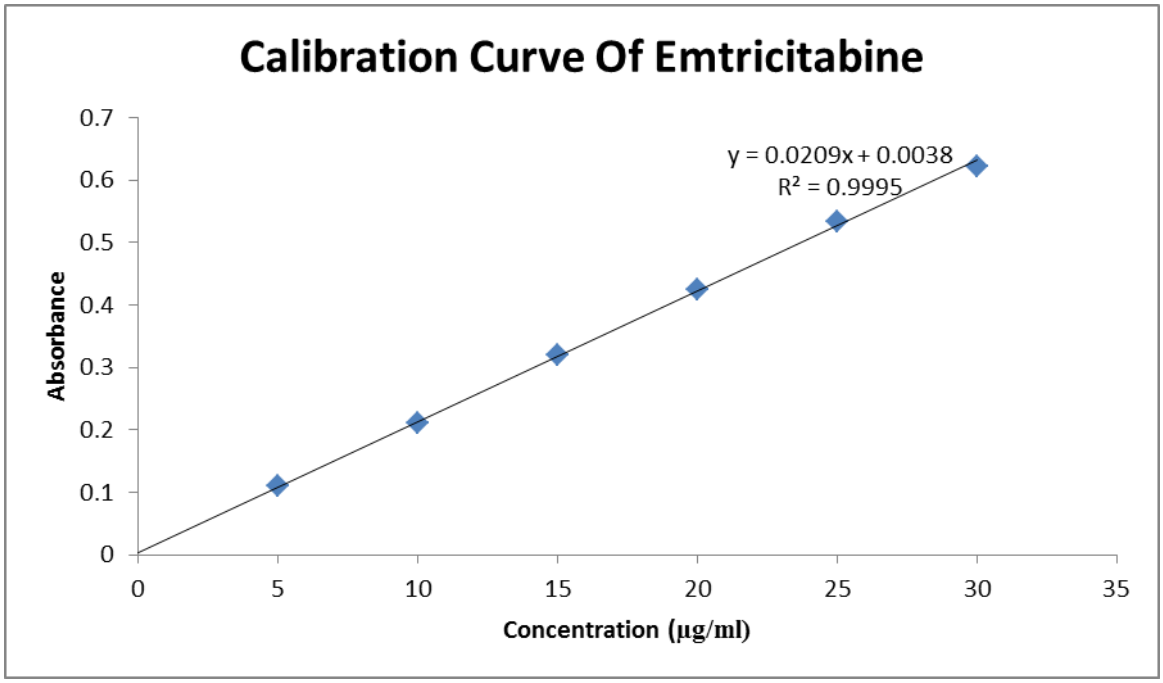
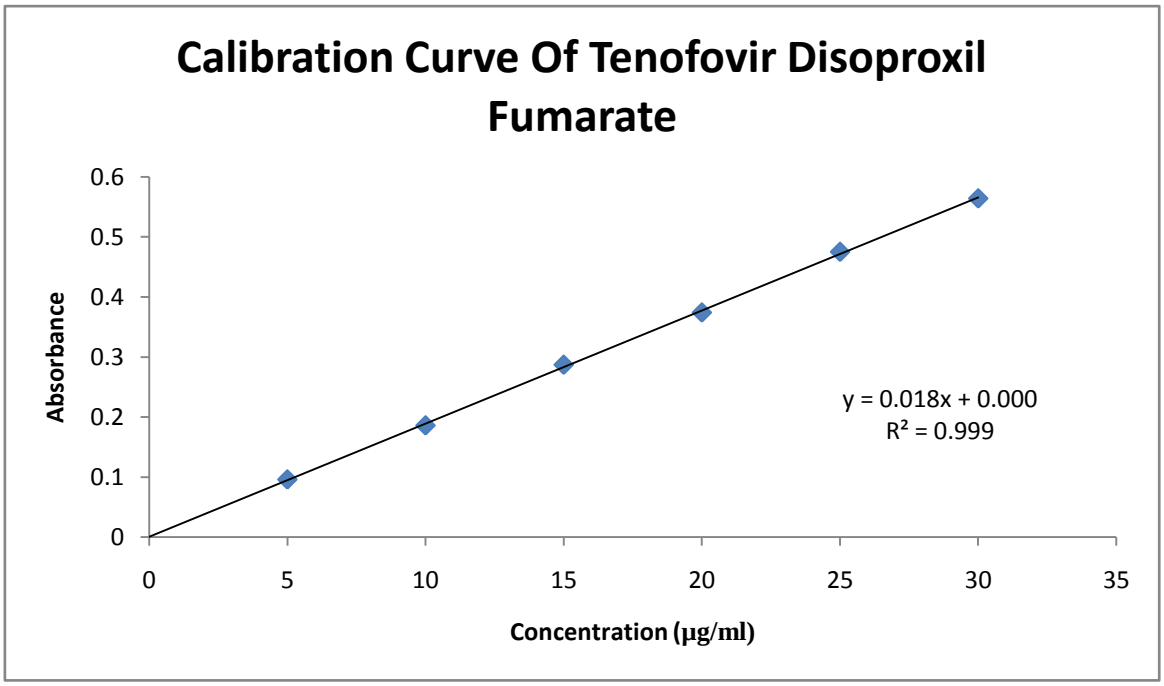


Figure-7 Calibration curve for Tenofovir Disoproxil Fumarate.



9.3 Evaluation of Lubrication Blend For Formulations

Table-28 Lubricated blend parameters

Formula	Angle of Repose	Bulk density g/ml	Tapped density g/ml	Compressibility Index %	Hausner Ratio
F1	35.89	0.57	0.67	14.923	1.175
F2	33.72	0.56	0.67	16.417	1.196
F3	22.61	0.54	0.64	15.625	1.185
F4	23.12	0.53	0.66	19.696	1.245
F5	24.57	0.53	0.64	17.187	1.207
F6	22.98	0.55	0.67	17.910	1.218
F7	23.14	0.56	0.66	15.151	1.178
F8	22.85	0.54	0.64	15.625	1.185
F9	23.08	0.57	0.65	12.307	1.140
F10	22.83	0.56	0.65	13.846	1.160

9.4DRUG CONTENT

FORMULATION (F3)

Assay

Emtricitabine =97.6 % w/w

Tenofovir disoproxil fumarate=98.8 % w/w

FORMULATION (F4)

Assay

Emtricitabine =97.9 % w/w

Tenofovir disoproxil fumarate=98.2% w/w

FORMULATION (F5)

Assay

Emtricitabine =98.7 % w/w

Tenofovir disoproxil fumarate=99.6 % w/w

FORMULATION (F6)

Assay

Emtricitabine =97.5 % w/w

Tenofovir disoproxil fumarate=98.9 % w/w

FORMULATION (F7)

Assay

Emtricitabine =99.2 % w/w

Tenofovir disoproxil fumarate=101.8 % w/w

FORMULATION (F8)

Assay

Emtricitabine =101.9 % w/w

Tenofovir disoproxil fumarate=102.1 % w/w

FORMULATION (F9)

Assay

Emtricitabine =99.7 % w/w

Tenofovir disoproxil fumarate=100.6 % w/w

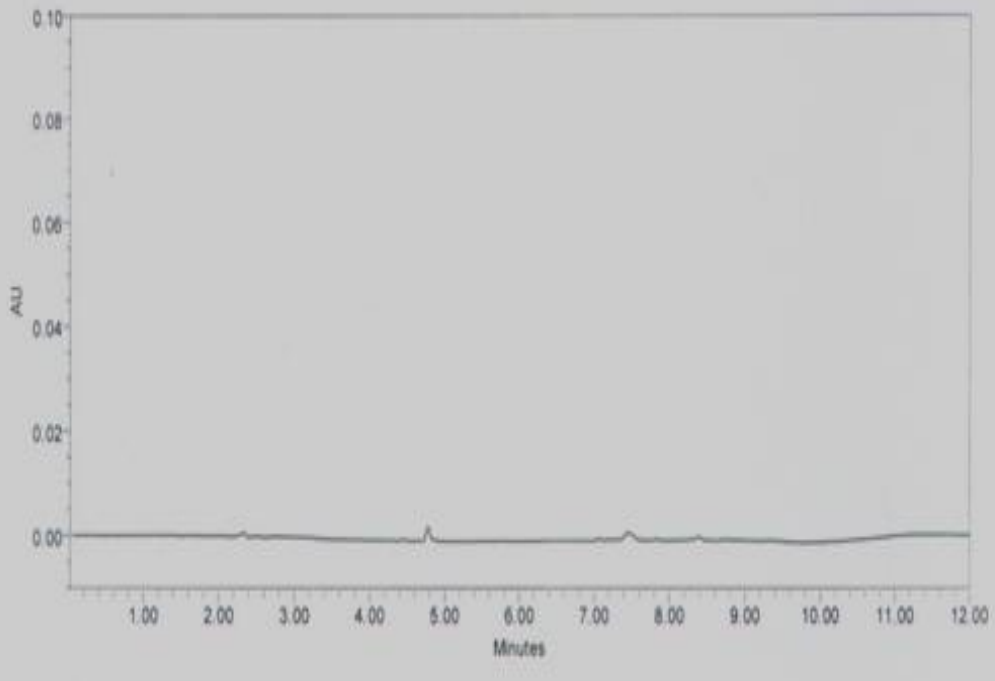
FORMULATION (F10)

Assay

Emtricitabine =101.7 % w/w

Tenofovir disoproxil fumarate=102.6 % w/w

Figure-8 .Assay of Blank



	Peak Name	Vial	RT
1	Emtricitabine	1	3.600
2	Tenofovir	1	5.700

Figure-9. Sample Injections 1 to 4

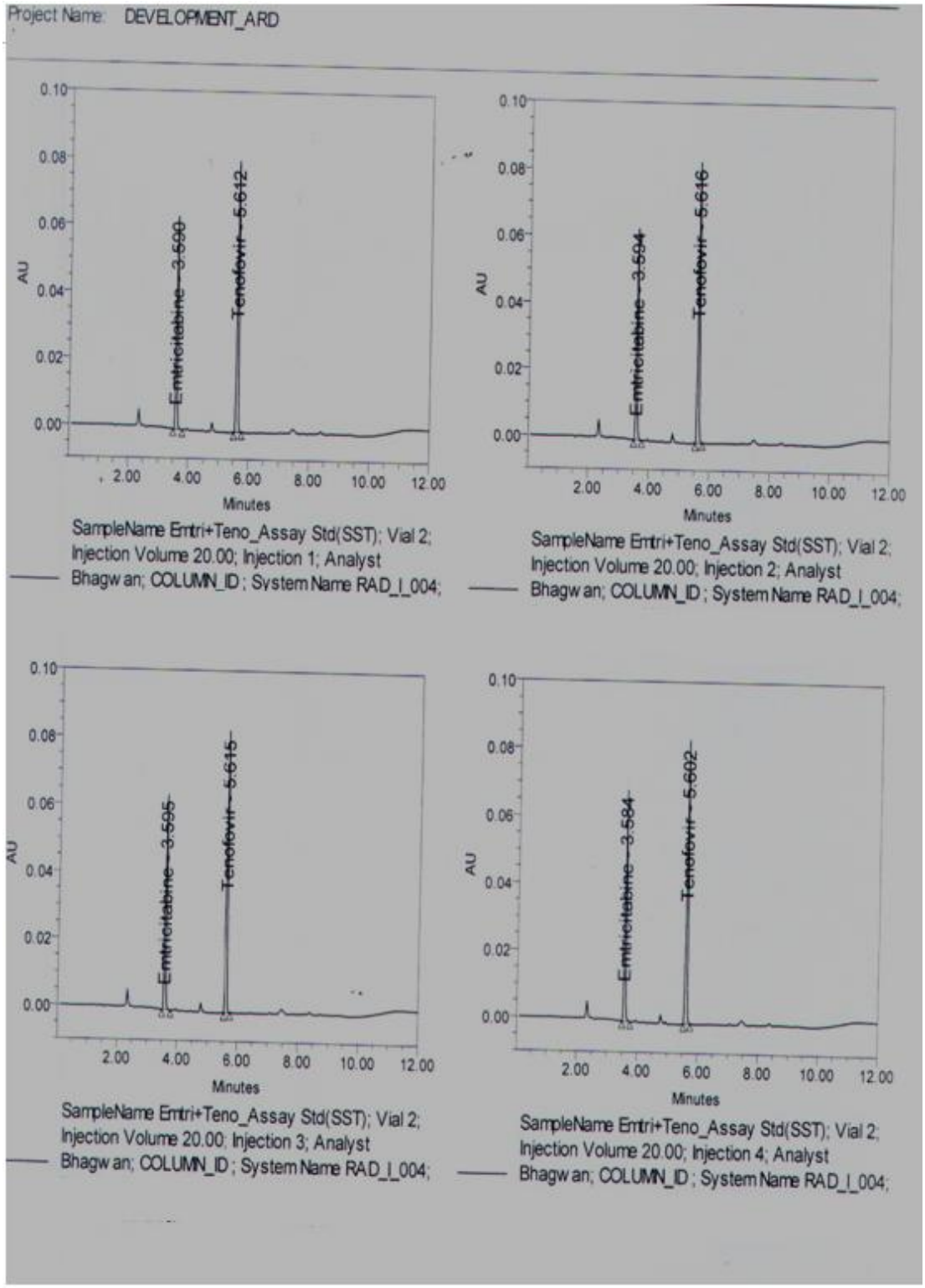
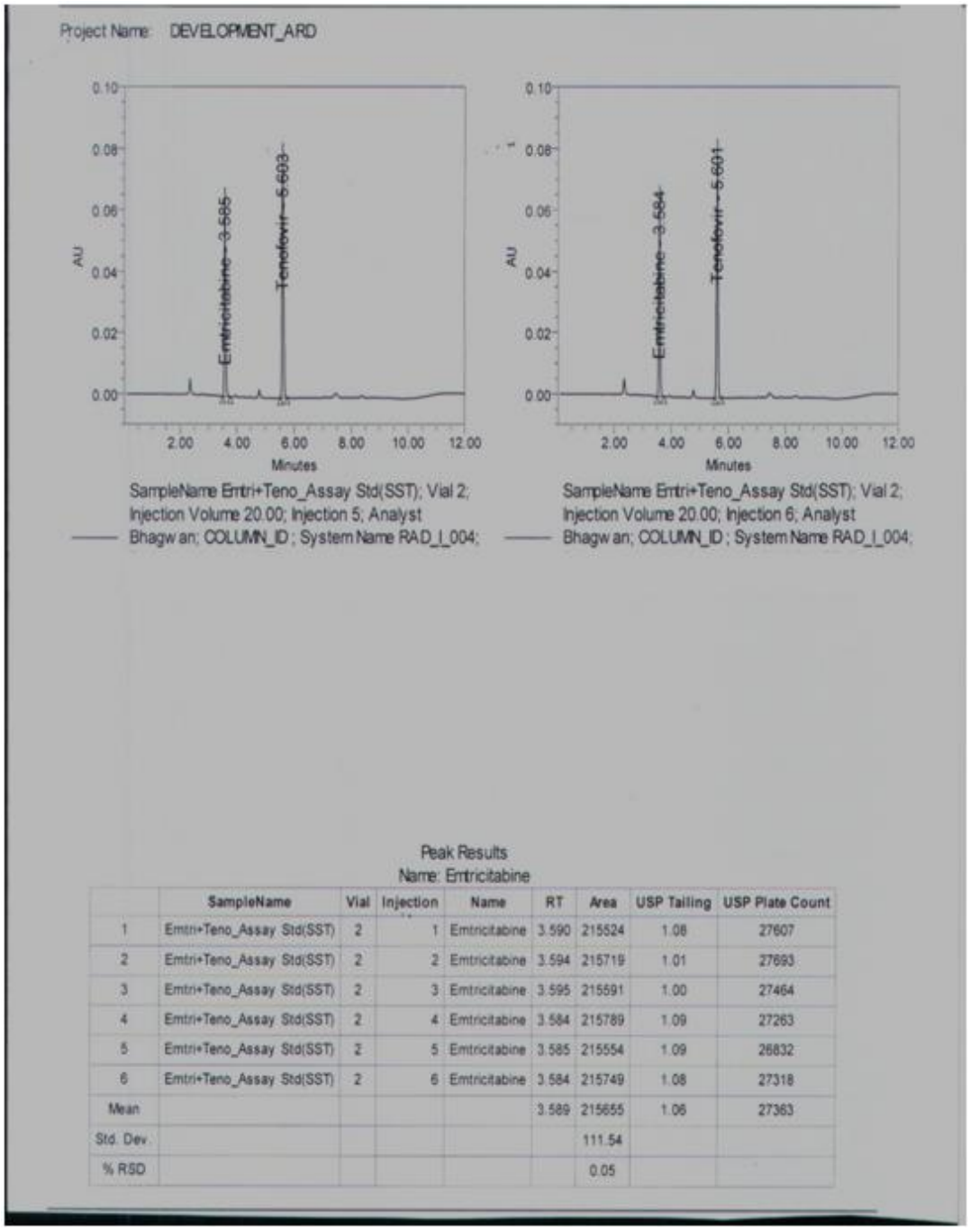


Figure-10.Sample Injections 5 to 6 and Peak results of emtricitabine



Peak Results
Name: Emtricitabine

	SampleName	Vial	Injection	Name	RT	Area	USP Tailing	USP Plate Count
1	Emtri+Teno_Assay Std(SST)	2	1	Emtricitabine	3.590	215524	1.08	27607
2	Emtri+Teno_Assay Std(SST)	2	2	Emtricitabine	3.594	215719	1.01	27693
3	Emtri+Teno_Assay Std(SST)	2	3	Emtricitabine	3.595	215591	1.00	27464
4	Emtri+Teno_Assay Std(SST)	2	4	Emtricitabine	3.584	215789	1.09	27263
5	Emtri+Teno_Assay Std(SST)	2	5	Emtricitabine	3.585	215554	1.09	26832
6	Emtri+Teno_Assay Std(SST)	2	6	Emtricitabine	3.584	215749	1.08	27318
Mean					3.589	215655	1.06	27363
Std. Dev.						111.54		
% RSD						0.05		

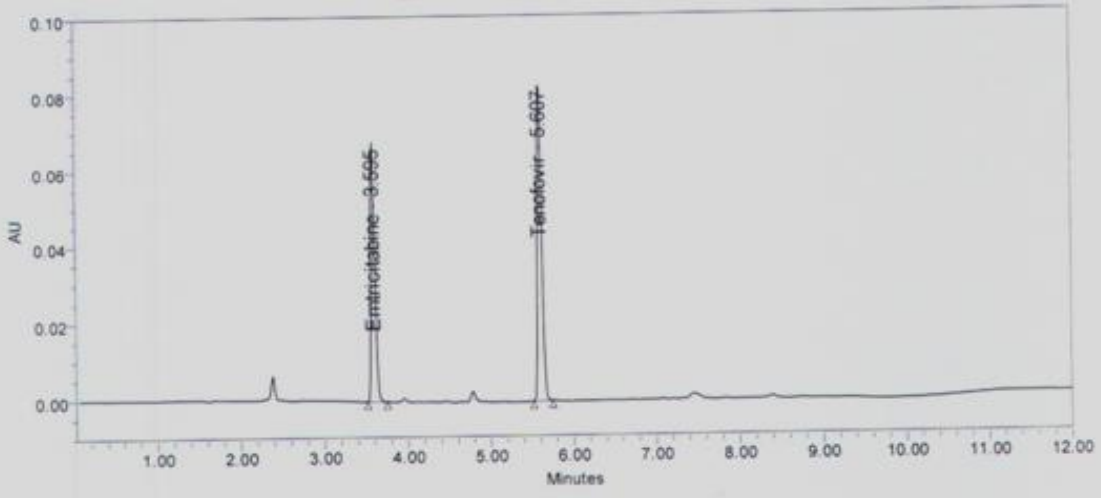
Figure-11: Peak results of Tenofovir disoproxil fumarate

Project Name: DEVELOPMENT_ARD

Peak Results
Name: Tenofovir

	SampleName	Vial	Injection	Name	RT	Area	USP Tailing	USP Plate Count
1	Emtri+Teno_Assay Std(SST)	2	1	Tenofovir	5.612	284322	1.02	56106
2	Emtri+Teno_Assay Std(SST)	2	2	Tenofovir	5.616	284815	1.04	59378
3	Emtri+Teno_Assay Std(SST)	2	3	Tenofovir	5.615	284442	1.03	58935
4	Emtri+Teno_Assay Std(SST)	2	4	Tenofovir	5.602	284697	1.09	59265
5	Emtri+Teno_Assay Std(SST)	2	5	Tenofovir	5.603	284098	1.08	57838
6	Emtri+Teno_Assay Std(SST)	2	6	Tenofovir	5.601	284225	1.08	59443
Mean					5.608	284433	1.06	58494
Std. Dev.						277.00		
% RSD						0.10		

Figure-12: Assay of Standard



	Peak Name	Vial	RT	Area	USP Resolution	USP Plate Count	USP Tailing	% Area
1	Emtricitabine	4	3.595	225513		28280	1.01	43.23
2	Tenofovir	4	5.607	296197	21.3	56903	1.07	56.77

9.5 Evaluation Of Core Tablets

Table-29Core tablet parameters

Formula	Weight (mg)	Thickness (mm)	Hardness (kg)	Friability (%w/w)	Disintegtration time(min)
F3	998± 1.0	6.90 ±0.5	24.1 ± 0.4	0.030 ± 0.01	27 min 48 sec ± 2 sec
F4	1001± 0.5	6.93 ±0.5	23.7 ± 0.5	0.034 ± 0.05	26 min 38 sec ± 3 sec
F5	1004± 0.4	6.96 ±0.5	23.5 ± 0.3	0.035 ± 0.05	22min 28 sec ± 3 sec
F6	995 ± 1.5	6.98 ±0.8	23.1 ± 0.5	0.039 ± 0.07	25min 48 sec ± 4 sec
F7	1011± 1.0	6.99 ± 0.5	22.9 ± 0.3	0.034±0.03	21min 57 ± 2 sec
F8	1000± 1.5	7.09±0.4	22.3 ± 0.5	0.048 ± 0.03	7min 38 sec ± 3 sec
F9	999 ± 0.5	7.03 ± 0.5	22.1 ±0.5	0.045 ±0.05	13min 57 ±5 sec
F10	1013± 0.5	7.01 ± 0.5	22.4 ±0.5	0.043 ±0.05	7 min 34 sec ± 3 sec

9.6Evaluation Of CoatedTablets

Table-30 Coated tablet parameters

Formula	Weight (mg)	Thickness (mm)	Hardness (kg)	Disintegtration time(min)
F3	1030 ± 1.5	7.4 ±0.5	25.4 ± 0.4	29min 26 sec ± 2.0 sec
F4	1033 ± 0.8	7.4 ±0.9	24.9 ± 0.5	28min 10 sec ± 3.0 sec
F5	1028± 1.7	7.3 ±0.7	24.5 ± 0.3	24 min10 sec ± 7 sec
F6	1026 ± 2.5	7.3 ±0.4	24.4 ± 0.5	27 min15 sec ± 1.0 sec
F7	1035 ±1.2	7.4 ±0.5	24.1 ± 0.3	23min 40 sec ± 5sec
F8	1034 ± 1.0	7.5 ±0.5	23.8 ± 0.5	9min 30 sec ± 6 sec
F9	1033 ±2.5	7.5 ±0.3	23.6 ±0.5	15min 54 sec ± 5sec
F10	1032 ±1.5	7.6 ±0.8	23.9 ±0.5	9min 22 sec ± 3sec

Figure-13 Coated Tablets Thickness of Different Formulations

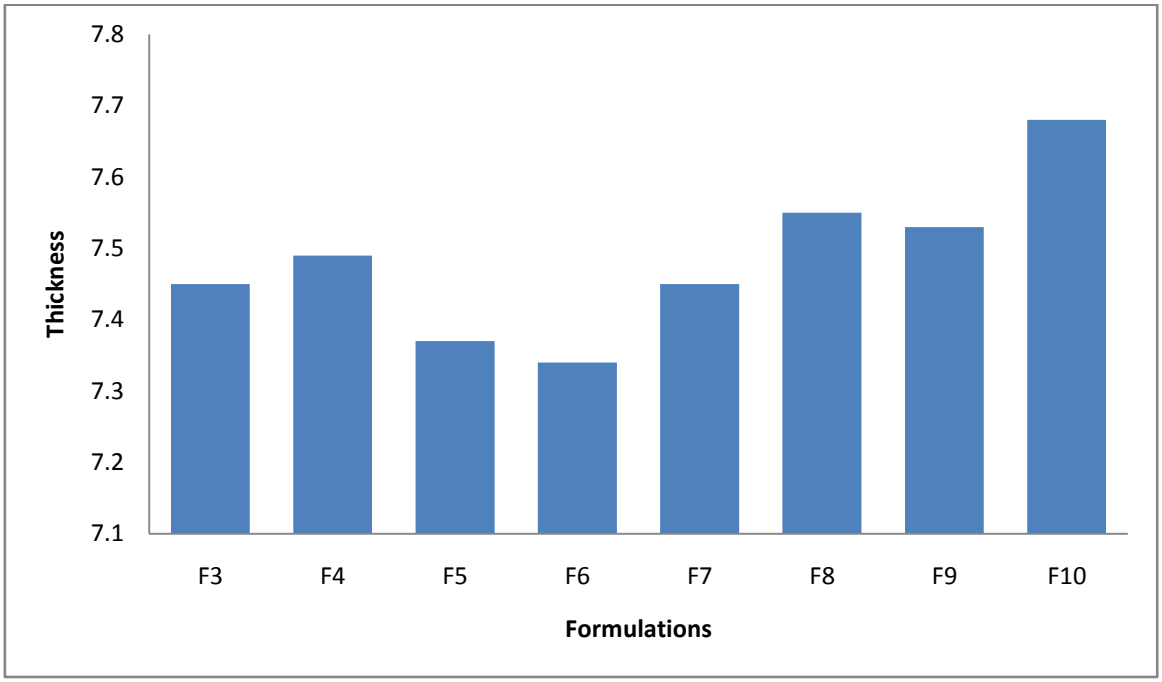


Figure-14 Coated Tablet Hardness Of Different Formulations

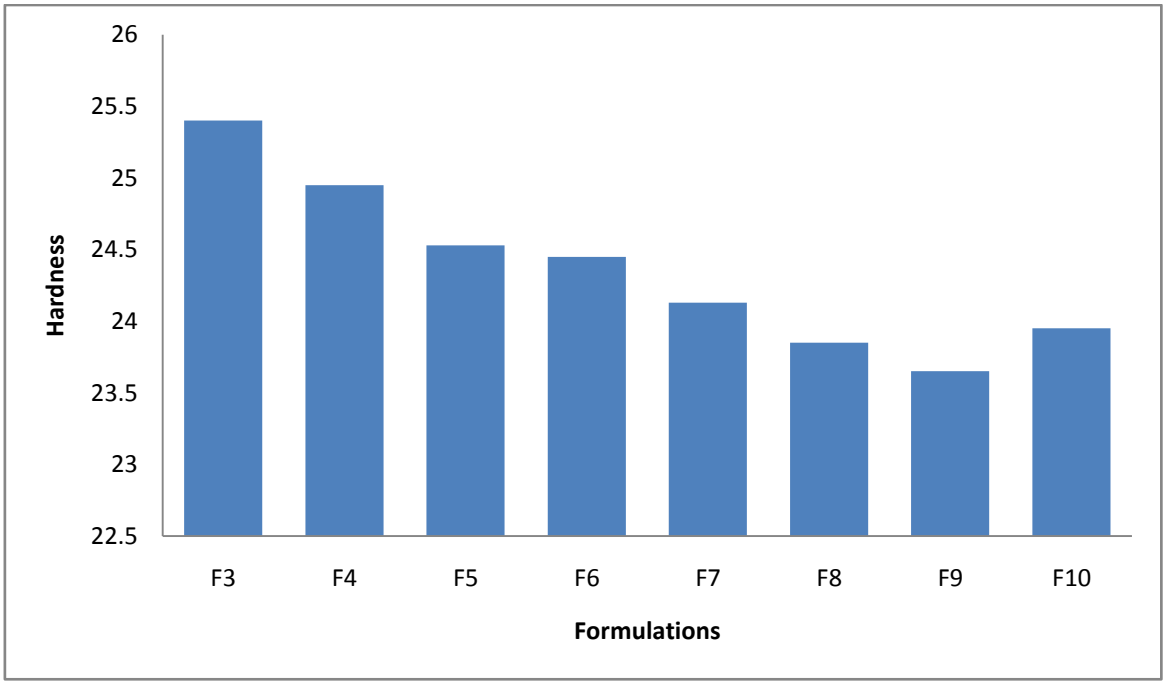
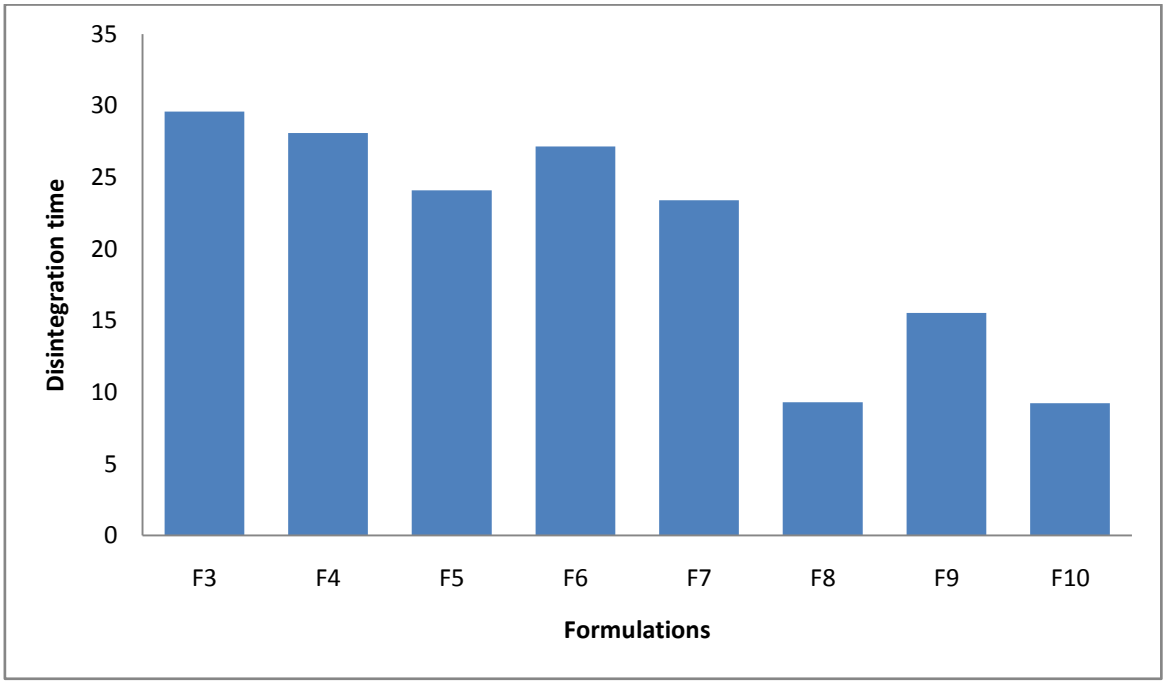


Figure-15 Coated Tablet Disintegration Time oF Different Formulations



9.7 Dissolution Profile

Table-31*In-vitro* drug Release Profile for*INNOVATOR*(Emtricitabine)

Time(Minutes)	Cumulative Percentage Drug Release of Emtricitabine
0	0
5	31.0
10	64.4
15	73.3
30	97.0
45	98.0

Figure-16 In vitro drug release profile of Innovator(Emtricitabine)

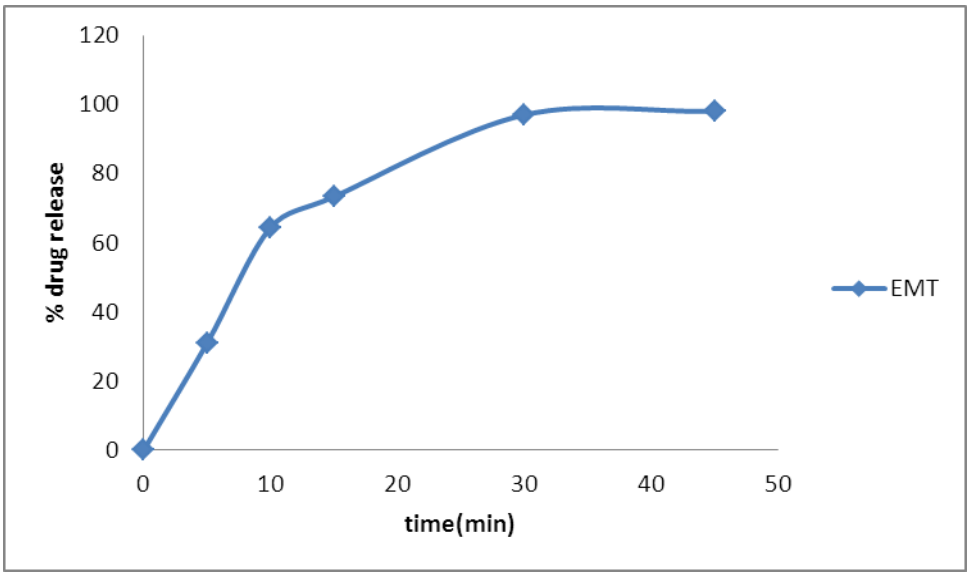


Table-32*In-vitro* drug Release Profile for *INNOVATOR* product (Tenofovir disoproxil -fumarate)

Time (Minutes)	Cumulative Percentage Drug Release of Tenofovir disoproxil fumarate
0	0
5	33
10	65.8
15	73.9
30	95.6
45	96.8

Figure-17In vitro drug release profile of Innovator(Tenofovir)

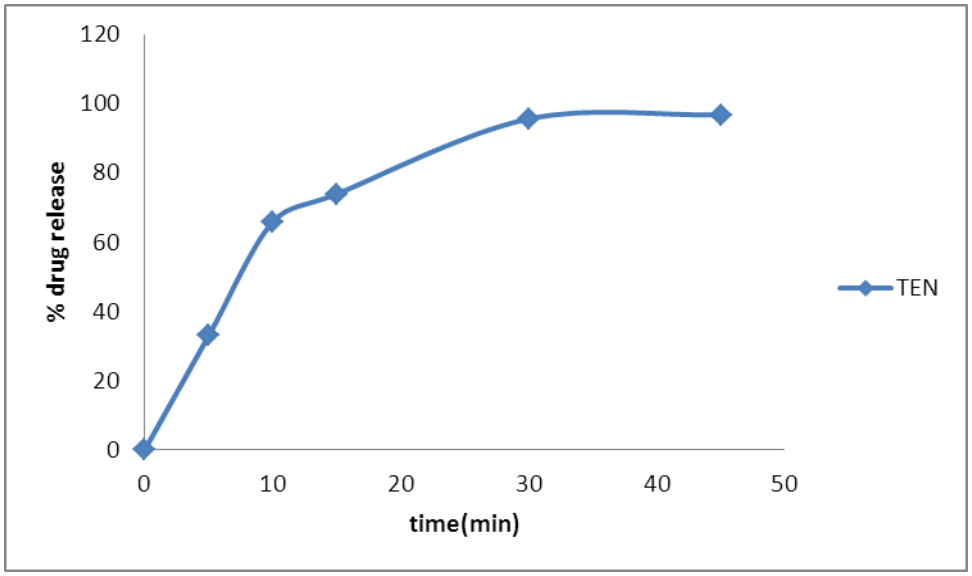


Table-33*In-vitro* release of Emtricitabine of formulations

Time (min)	Cumulative % Drug release							
	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0
5	20	21	22.4	22	24.1	34	32.5	33.2
10	33.9	34.1	35.1	34.9	36.8	68.1	63.4	66.3
15	41.5	42.4	45.4	44.1	47.5	83.4	78.1	84.1
30	67.9	68.3	70.3	69.8	72.6	97.1	93.8	97.4
45	86.9	87.2	89.1	88.3	92.1	99.8	95.9	99.8

Figure-18DissolusionOf Emtricitabine Formulations With Innovator

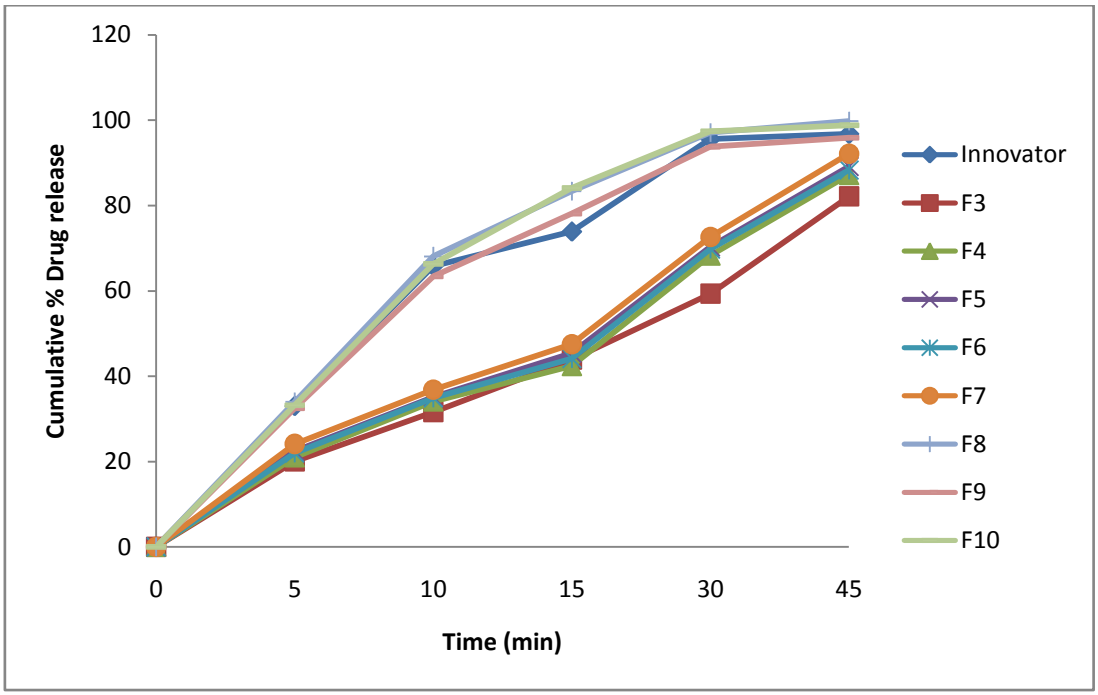
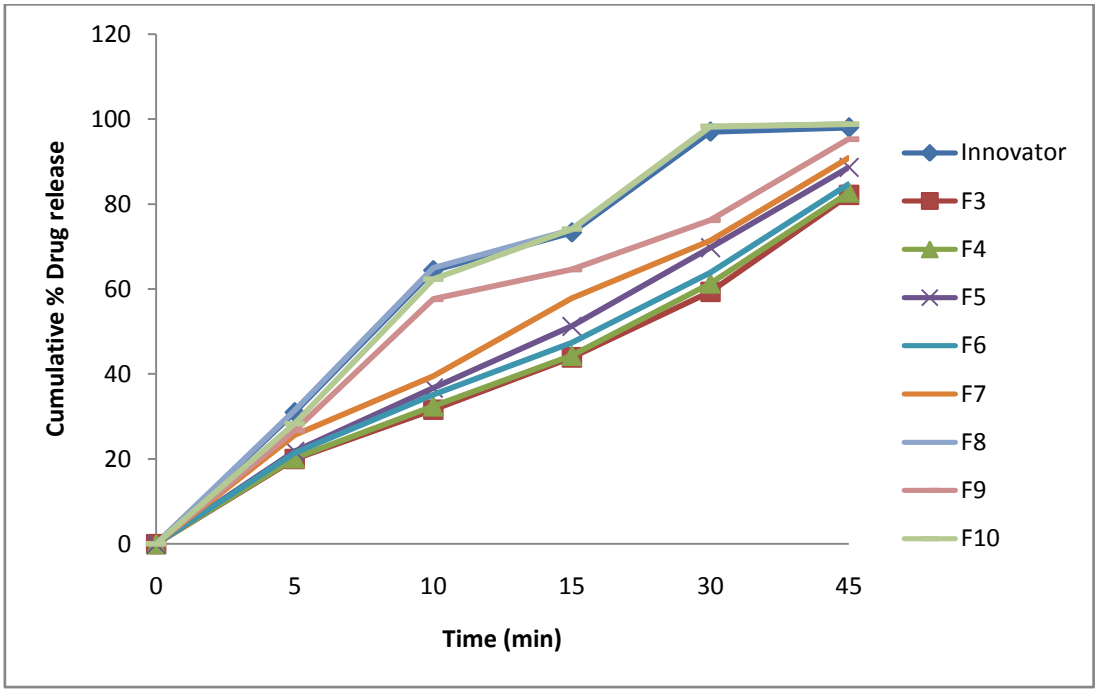


Table-34*In-vitro* release of Tenofovir disoproxil fumarate formulations

Time (min)	Cumulative % Drug release							
	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0
5	20.0	20.2	21.8	21.4	25.6	31.4	26.7	28.3
10	31.6	32.4	36.7	35.1	39.5	65	57.6	62.3
15	43.9	44.3	51.2	47.3	57.8	73.9	64.6	74.1
30	59.3	61.3	69.7	63.8	71.4	98.1	76.2	98.3
45	82.1	82.7	88.6	84.7	90.9	98.8	95.3	98.8

Figure-19Dissolusion Of Tenofovir Disoproxil Fumarate Formulations with Innovator



9.8kinetic Release Profile Data For Optimization Batch(F8)

Table 35 Kinetic values of Emtricitabine

S. no	Time(min)	Square root of time	Log time	Cum % drug release	Log Cum % drug release	Cum % drug remaining	Log Cum % drug remaining
1	0	0	0	0	0	100	2
2	5	2.23	0.698	34	1.53	66	1.82
3	10	3.16	1	68.1	1.83	31.9	1.50
4	15	3.87	1.17	83.4	1.92	16.6	1.22
5	30	5.48	1.47	97.1	1.98	2.9	0.46
6	45	6.71	1.65	99.8	1.99	0.2	-0.69

Figure20: Zero order plot(Emtricitabine)

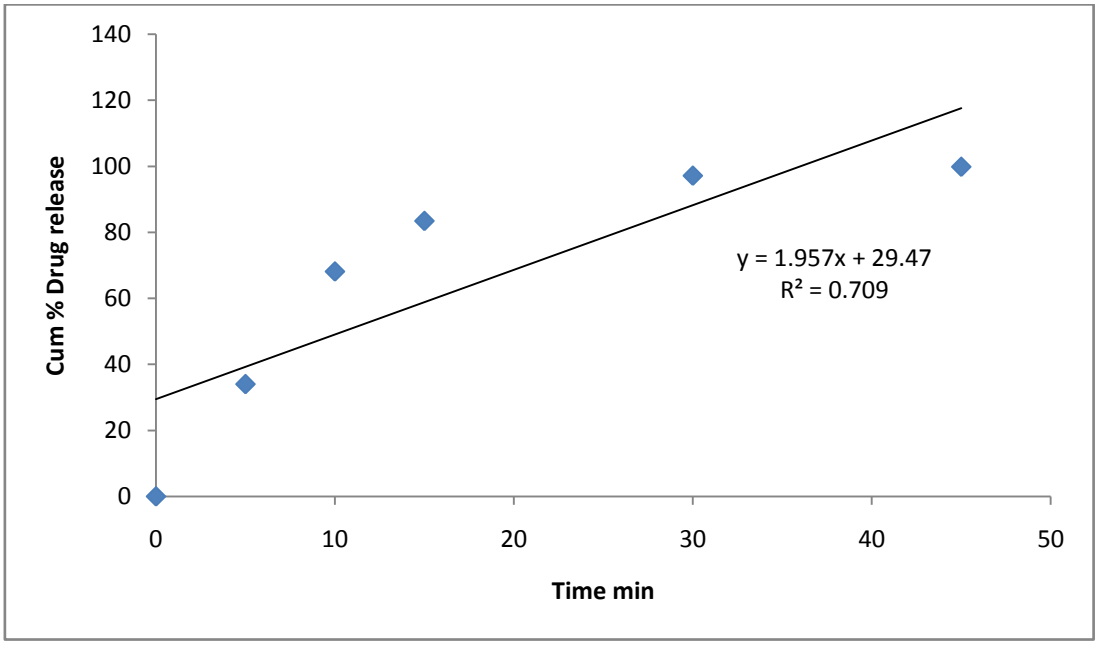


Figure 21:First order plot(Emtricitabine)

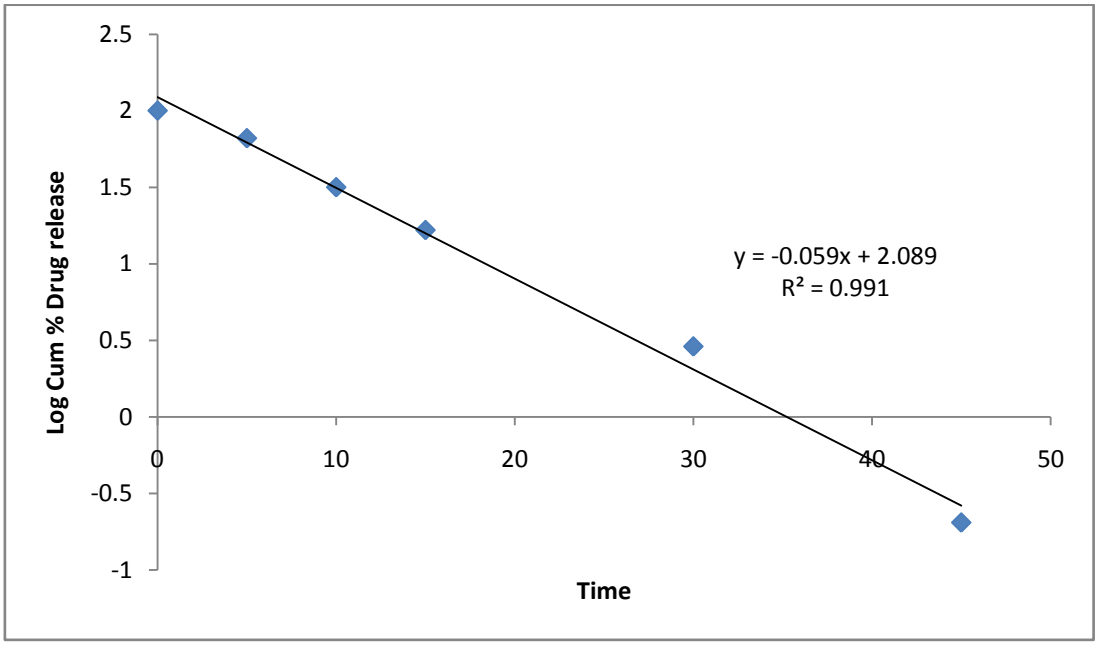


Figure 22:Higuchi plot (Emtricitabine)

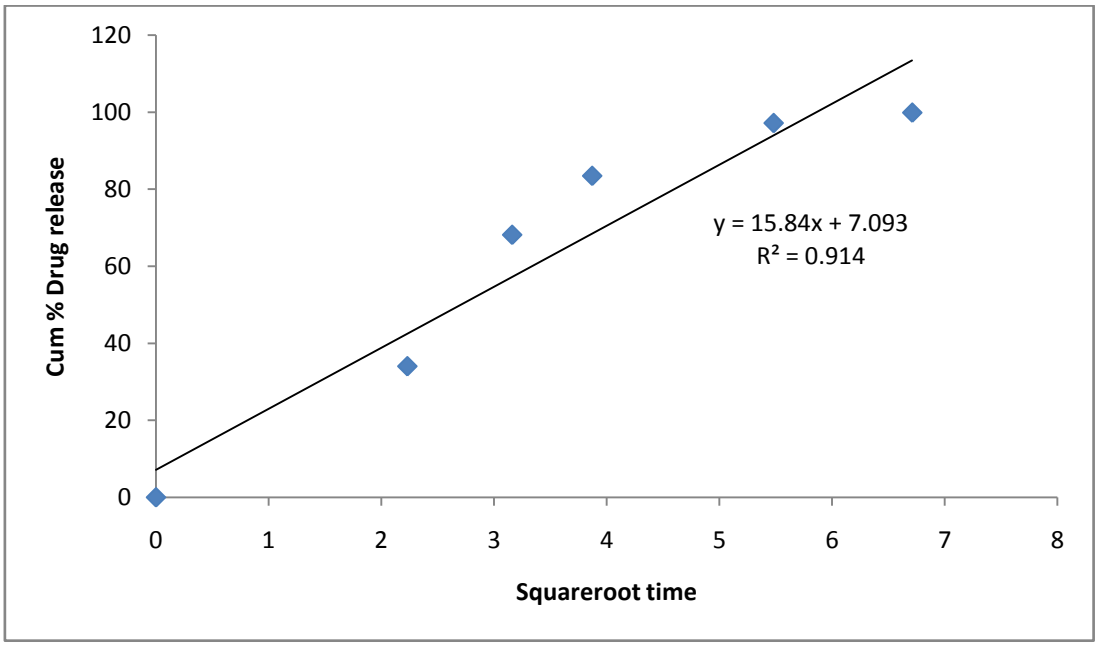


Figure23:Korsmeyerpeppas plot (Emtricitabine)

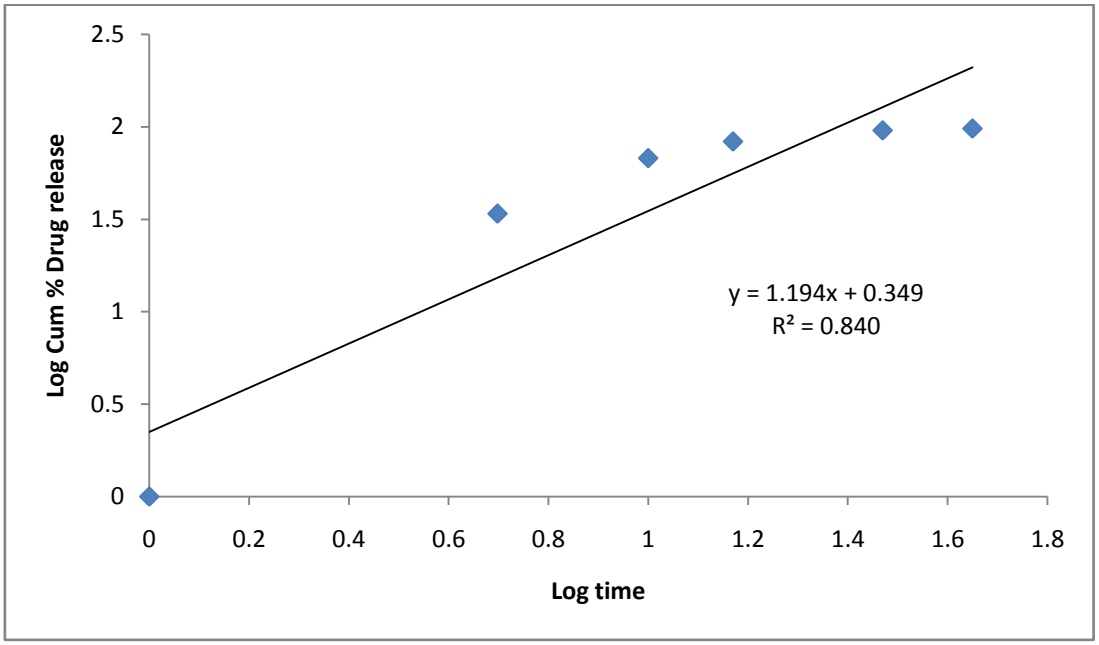


Table 36: Kinetics values obtained different plots of Formulation (F8) of Emtricitabine.

Formulation	Zero order plot(R^2)	First order plot(R^2)	Higuchi plot (R^2)	Korsmeyer plot(R^2)	
				R^2	N
F8	0.7669	0.9889	0.9436	0.8555	1.1948

Table 37: Kinetc values of Tenofovir Disoproxil Fumarate

S.no	Time(min)	Square root of time	Log time	Cum % drug release	Log Cum %drug release	Cum % drug remaining	Log Cum % drug remaining
1	0	0	0	0	0	100	2
2	5	2.23	0.69	31.4	1.49	68.6	1.83
3	10	3.16	1	65	1.81	35	1.54
4	15	3.87	1.17	73.9	1.86	26.1	1.41
5	30	5.48	1.47	98.1	1.99	1.9	0.27
6	45	6.71	1.65	98.8	1.99	1.2	0.07

Figure 24: Zero order plot(Tenofovir Disoproxil Fumarate)

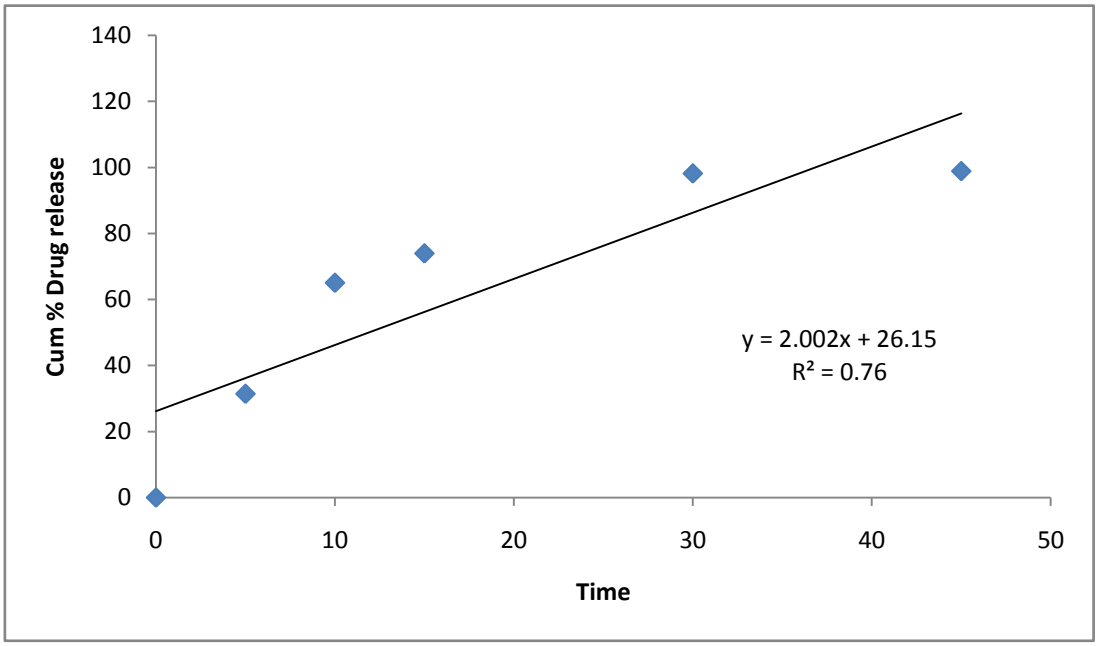


Figure 25: First order plot (Tenofovir Disoproxil Fumarate)

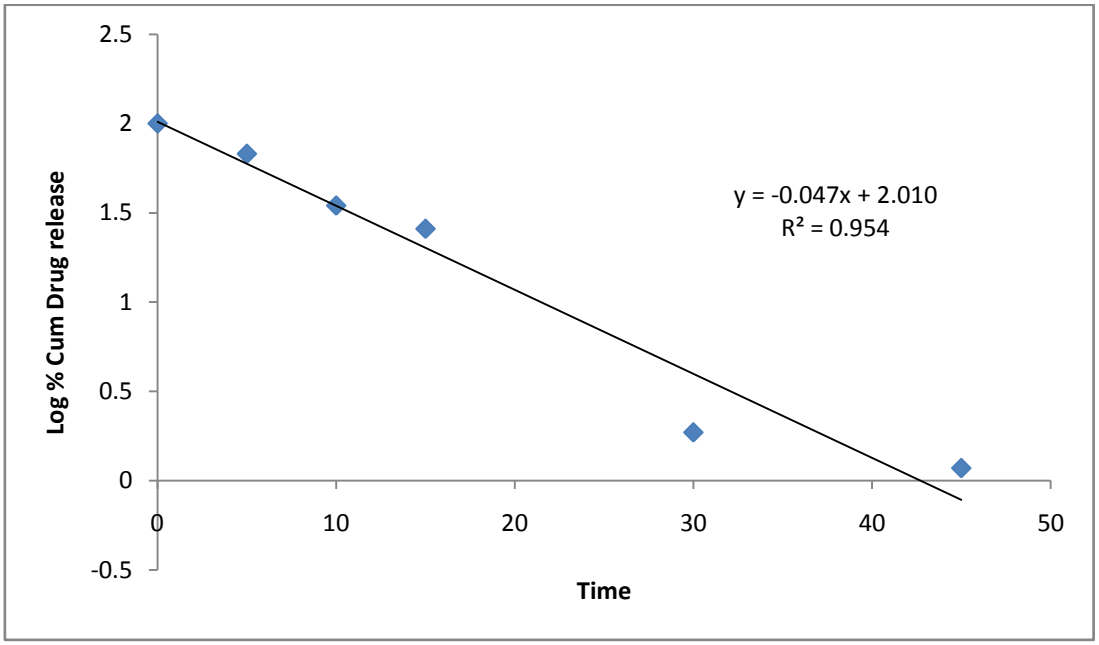


Figure 26: Higuchi order plot (Tenofovir Disoproxil Fumarate)

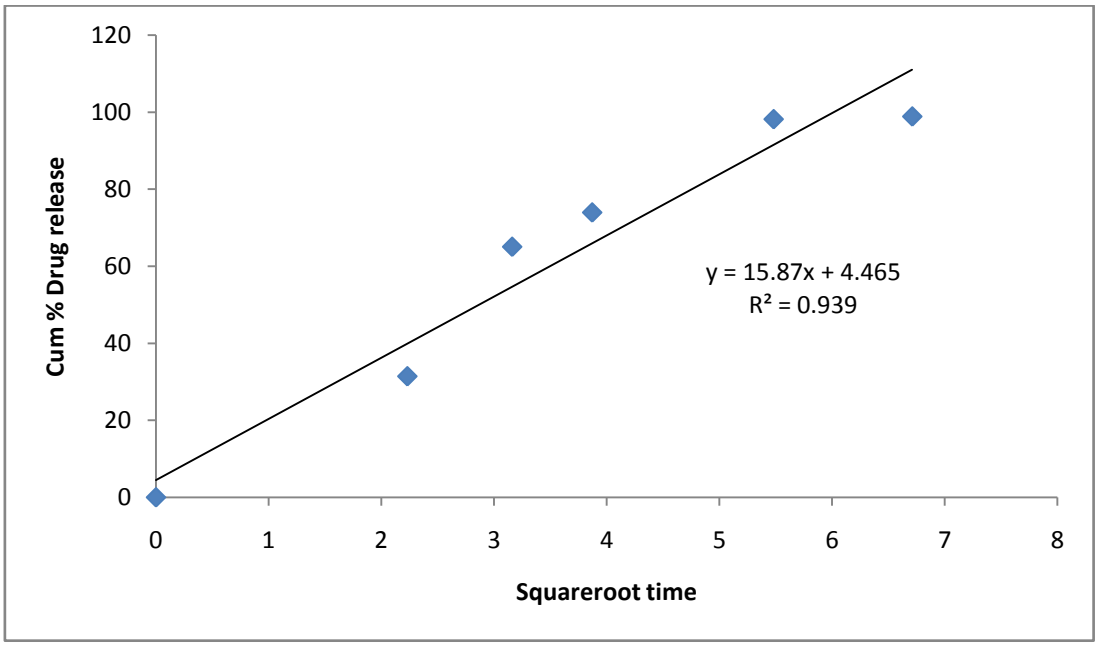


Figure 27: Korsmeyer plot (Tenofovir Disoproxil Fumarate)

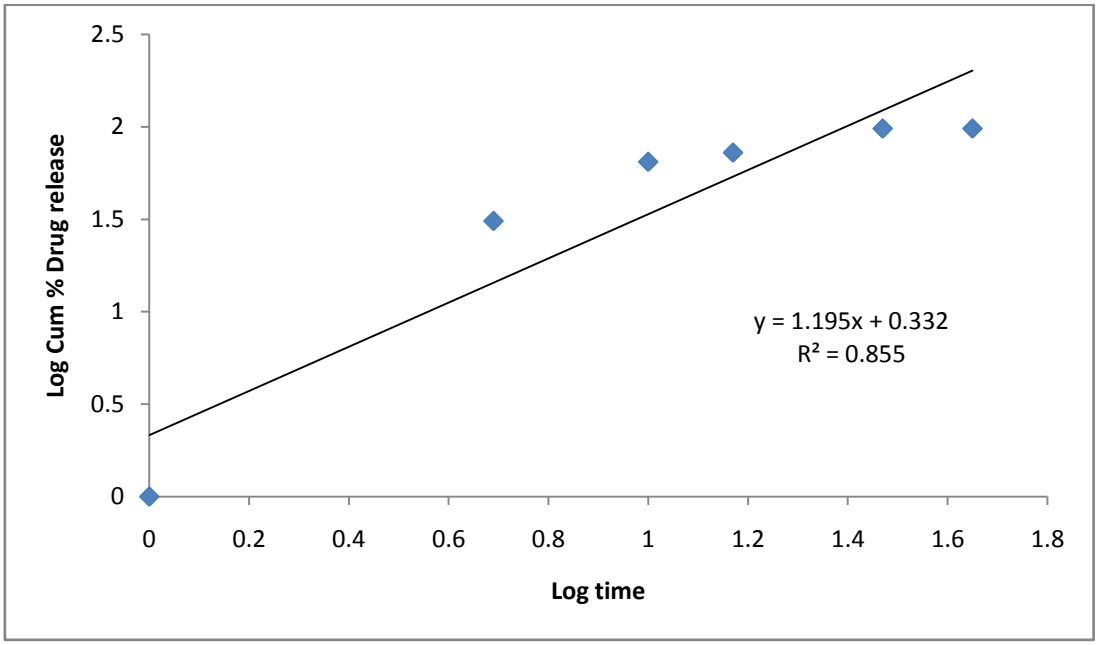


Table 38: Kinetics values obtained from different plots of formulation (F8) ofTenofovir Disoproxil Fumarate.

Formulation	Zero order plot(R^2)	First order plot(R^2)	Higuchi plot (R^2)	Korsmeyer plot(R^2)	
				R^2	N
F8	0.7020	0.9809	0.9105	0.8401	1.1952

9.9 STABILITY STUDIES

Condition: 25°C/60%RH

40°C/75%RH

Table-39: Stability Studies

S.No	Parameters	Conditions			
		Initial	40C& 75%RH	40C& 75%RH	40C& 75%RH
		0 Day	1 month	2 month	3 month
1	Average weight	1030±5(mg)	1030±5(mg)	1030±5mg	1030±5mg
2	Thickness(mm)	7.4±0.9	7.4±0.9	7.4±0.8	7.4±0.8
3	Hardness(kg)	24.0±0.5	25.0±0.4	25.0±0.1	25.0±0.1
4	Disintegration(min)	9min10sec	11min09sec	11min03sec	11min03sec
5	Dissolution(45 min)	99.7,95.8	99.6,95.8	99.4,95.2	99.2,95.0
6	Assay(%)	99.8,100.9(%%w/w)	99.8,100.9(%w/w)	99.7,100.2(%w/w)	99.7,99.98(%w/w)

S.no	Parameters	Initial	25^0C&60%RH
		0 Day	3 month
1	Average weight	1030±5(mg)	1030±5mg
2	Thickness(mm)	7.4±0.9	7.4±0.8
3	Hardness(kg)	24.0±0.5	25.0±0.3
4	Disintegration(min)	9min10sec	11min09sec
5	Dissolution(45min)	99.7,95.8	99.4,95.9
6	Assay(%)	99.8,100.9(%w/w)	99.7,100.8(%w/w)

10.**DISCUSSION**

The prepared granules were evaluated for the angle of repose which was ranged from 35.89 to 22.83 for the different formulation, the bulk density was found to be 0.57 to o.53 and the hausner's ratio was ranged from 1.245 to 1.140.

The drug content was analyzed by using HPLC the readings were as per I.P limit ranging from 97.6%w/w to 102.1 % w/w.

Formulations (F1, F2, F3) are prepared for the selection of the process. The . formulation F1 was not selected due to high angle of repose value(35.89). the result revealed that the powder blend may not be suitable for the direct compression method.

The granules of formulation f2 was prepared by dry granulation method and the results was found low granules strength. the result revealed that the powder blend may not be suitable for the dry granulation method.

the granules of formulation F3 was prepared by wet granulation. water is used as a vehicle.the result of granules were found Good strength, flow property but impurities like monoesters were formed above the limit (1.4%). The disintegration time was found to be 29 min 26 sec with starch 1500(10%) as disintegrant and the percentage of drug release at the end of 45 min of Emtricitabine and Tenofovir disoproxil fumarate was found to be 82.1% and 86.9%. The results found were not matching with the innovator.

So in the next formulation F4, the vehicle was changed to mixture of IPA and Water (80:20). With this the impurities formed was reduced to 0.562%. But there is not much change in disintegration time and %of drug release than with formulation F3 where starch (10%) was used as a disintegrant for both.

So, for further formulations F5-F10 the same wet granulation with IPA and water (80:20) was selected . But to reach the target disintegration time (11min 30 sec) and %of drug release (98% for ECB and 96.8% TDF) as that of innovator differentdistintegrants (starch 1500, lycatab C, HPCLH-11) with different concentration (8%, 10% and 12%) was used.

In the formulation F5 Starch1500 (12%) was used. The disintegration time was found to be 27 min 38 sec. The percentage of drug release of Emtricitabine and Tenofovir disoproxil fumarate was found to be 89.1% and 88.6% .

To increase the drug release and to decrease the disintegration time the formulation F6 was prepared by changing the disintegrate to Lycatab-c (10%). The disintegration was found to be 25 min 48 sec and the percentage of drug release was found to be 88.3% for EMB and 84.7% for TDF. Further in the formulation F7 the concentration of Lycatab C was increased to 12%. The disintegration time was found to be 23min 40 sec and the percentage of drug release was found to be 92.1% for EMB and 90.9% for TDF. Though, the percentage of drug release was increased but not matching with the innovator.

In the formulations F8,F9& F10 HPCLH-11 was used as a disintegrant at 10%,8% and 12% respectively. The disintegration time for F8 was found to be 7 min 38 sec, for F9 was found to be 13 min 57 sec, and for F10 was found to be 7 min 34 sec.

The percentage of drug release for EMB was found to be 99.8%, 95.9%, 99.8% and for TDF it was found to be 98.8%, 95.3%, 98.2% for formulation F8,F9 and F10 respectively. This may be due to the wicking power of hydrophilic polymer-HPCLH-11.

The formulation F8 and F10 disintegration times and percentage of drug release reached the target innovator. So, the formulation F8 with concentration 10% of HPCLH-11 was selected as optimized formulation and further mechanism of drug release was calculated for formulation F8.

Results of the kinetics of drug release shows that both the drugs EMB and TDF were best fit into the first order kinetics. Korsmeyerpeppas was calculated to find out the mechanism of release. The n values was found to be 1.1952 for EMB and1.1948 for TDF it indicates non-fickian super case II transport so, the drug release may be by the erosion of polymeric chain.

Stability studies were performed for a period of 3 months. Samples are analysed initial 1st month 2nd month and 3rd month storing the tablets at 40^{0}C and 75% RH. At 25^{0}C & 60% RH the samples were analysed. It was found that ther was no physical and chemical change based on initial data.

11. SUMMARY AND CONCLUSION

SUMMARY

The main aim of the present study is to develope and evaluates Emtricitabine combination with tenofovir disoproxil fumarate comparable to the marketed product.

The compatibility test shows no intraction with the drug and excipients . The process selected was wet granulation. The formulations was optimized by using different disintegrants (Starch1500,Lycatab C and HPCLH-11) at different concentrations (8%,10%&12%). All the formulations were evaluated for physical characteristics, disintegration, invitro dissolution and stability studies. Based on results formulation F8 with HPCLH-11(10%) selected as best formulation since it matches with innovator product.

Stability studies were performed for these batches 1-3 months under accelerated and long term testing conditions. During that period the product was analysed for physical appearance, hardness, thickness, friability, dissolution, assay and related substances. The results were found to be within the specified limit.

The selection of manufacturing process to the finalization of pack has been done in according with recognized principles of current good manufacturing process and relevant FDA guidelines and pharmacopoeia.

CONCLUSION

The immediate release tablets of Emtricitabine combination with Tenofovir disoproxil fumarate have been developed with wet granulation method with serial increasing Disintegrant concentration ratio in each subsequent batch. And it is compared with that of Marketed(Truvada) tablets. Various trials were performed to get the optimized formula with Disintigrent HPCLH-11. Among all the design formulations F8 is showing optimized (acceptable) results within USP limits. There is no undesirable change is found in accelerated stability condition for 1&3 months in optimized formulated batch.

From the above all Formulations and observations we conclude that batch no F8 is showing result with in USP limits and same like Innovator. So further *in vivo* studies can be performed

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